CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040111

Trade Name : PROCAINAMIDE HCL EXTENDED RELEASE TABLETS 1000MG

Generic Name: Procainamide Hcl Extended Release Tablets 1000mg

Sponsor : COPLEY PHARMACEUTICALS, INC.

Approval Date: December 13, 1996

ANDA 40-111

DEC 13 1996

Copley Pharmaceutical Inc.
Attention: W.E. Brochu, Ph.D.
Canton Commerce Center
25 John Road, Canton, MA 02021

Dear Dr. Brochu:

This is in reference to your abbreviated new drug application dated July 5, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Procainamide Hydrochloride Extended-release Tablets USP, 1000 mg.

Reference is also made to your amendment dated October 26, 1995, April 19 1996 and June 14, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Procainamide HCl Extended-release Tablets USP, 1000 mg, are bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Procan SR™ Tablets, 1000 mg, of Parke-Davis, Division of Warner Lambert Co.).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution test and tolerances are:

Meets USP Drug release Test 5:

	Time	% released
Acid stage:	1 hour:	between
Buffer stage:	4 hours:	between
	6 hours:	between
	8 hours:	NLT

The interim dissolution specifications should be finalized by submitting a supplemental application containing dissolution data for the first three production size batches produced post-approval. The supplemental application should be submitted under 21 CFR 314.70 (c)(1) when there are no revisions to the interim

specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplemental application should be submitted under 21 CFR 314.70 (b)(2)(ii).

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission. We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

10/13/96

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO#3

2. ANDA 40-111

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical Inc.
Attention: Jerome P. Skelly, Ph.D.
Canton Commerce Center
25 John Road, Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION
Procan SR, 1000 mg Parke Davis (Division of Warner Chilcott). There are no patents listed for this tablet. Exclusivity has not been granted for Procan Extended-release tablets.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Procainamide Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Firm:
July 5, 1994: Original Submission
May 8, 1995: Amendment
April 18, 1996: Bio amendment
June 14, 1996: Amendment

FDA:
August 19, 1994: Acknowledgement letter
January 23, 1995: Deficiency letter
September 14, 1995: Bio. deficiency letter
November 8, 1995: Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

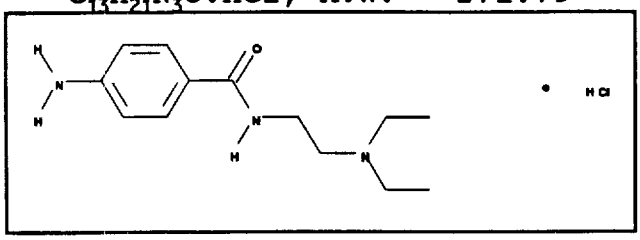
13. DOSAGE FORM
Extended-release Oral Tablet

14. POTENCY
1000 mg

15. CHEMICAL NAME AND STRUCTURE

Procainamide Hydrochloride USP

$C_{13}H_{21}N_3O.HCl$; M.W. = 271.79



p-Amino-N-[2-(diethylamino)ethyl]benzamide monohydrochloride.
CAS [614-39-1]

16. RECORDS AND REPORTS
Debartment Certification is submitted on page 5.
Procainamide Hydrochloride Extended Release Tablets 750 mg approved on 3/23/87. The formulation of Copley Procainamide HCl Extended-release Tablet USP, 750 mg (89-438) is proportional to that of the 1000 mg strength. (500 mg 88-974 approved on July 22, 1985).

17. COMMENTS
The application is approvable pending receipt of acceptable EER.

18. CONCLUSIONS AND RECOMMENDATIONS
The application can be approved based on acceptable EER.

19. REVIEWER: Sema Basaran, Ph.D.
DATE COMPLETED: 11-8-96

NDC 38245-117-10

PROCAINAMIDE HYDROCHLORIDE *Extended-release* TABLETS, USP

1000 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Copley Pharmaceutical, Inc.
Canton, MA 02021

USUAL DOSAGE: See package insert for complete prescribing information.

Patients should not break or chew tablets.

Each Extended-release Tablet Contains:
Procainamide Hydrochloride, USP . . 1000 mg

Dispense in a tight container as defined in the USP.

Keep this and all drugs out of the reach of children.

Store at controlled room temperature, 15°-30° C (59°-86° F). Protect from moisture.

Note: The drug in Procainamide Hydrochloride Extended-release Tablets is "held" in a wax core that has been designed to slowly release the drug into your system. When this process is completed, the empty wax core is eliminated from your body. Do not be concerned if you occasionally notice something that looks like a tablet in your stool.

N 3 38245-117-10 9

RM 5343

LOT:

EXP:

NDC 38245-117-25

PROCAINAMIDE HYDROCHLORIDE *Extended-release* TABLETS, USP

1000 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

Copley Pharmaceutical, Inc.
Canton, MA 02021

USUAL DOSAGE: See package insert for complete prescribing information.

Patients should not break or chew tablets.

Each Extended-release Tablet Contains:
Procainamide Hydrochloride, USP . . 1000 mg

Dispense in a tight container as defined in the USP.

Keep this and all drugs out of the reach of children.

Store at controlled room temperature, 15°-30° C (59°-86° F). Protect from moisture.

Note: The drug in Procainamide Hydrochloride Extended-release Tablets is "held" in a wax core that has been designed to slowly release the drug into your system. When this process is completed, the empty wax core is eliminated from your body. Do not be concerned if you occasionally notice something that looks like a tablet in your stool.

N 3 38245-117-25 3

RM 5342

LOT:

EXP:

DEC

Procainamide Hydrochloride Extended-release Tablets, USP

LEA500000 Revised: January 1996

APPROVED

WARNING:
Positive ANA Titer: The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test, with or without symptoms of a lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefits versus risks of continued procainamide therapy should be assessed.

DESCRIPTION:
Procainamide hydrochloride, a Group 1A cardiac antiarrhythmic drug, is p-amino-N-[2-(diethylamino)ethyl]benzamide monohydrochloride, molecular weight 271.79. Its structural formula is:

*(focus for acetylation to N-acetylprocainamide)

Molecular formula:
$C_{13}H_{21}N_3O.HCl$.

Procainamide Hydrochloride Extended-release Tablets, meet USP Drug Release Dissolution Test 5.

Procainamide hydrochloride differs from procaine which is the p-aminobenzoyl ester of 2-(diethylamino)-ethanol. Procainamide as the free base has a pK_a of 9.23; the monohydrochloride is very soluble in water.

Procainamide Hydrochloride Extended-release Tablets are available for oral administration as pink, scored, film-coated tablets containing 500 mg procainamide hydrochloride; as tan scored, film-coated tablets containing 750 mg procainamide hydrochloride; and as red, scored film-coated tablets containing 1000 mg procainamide hydrochloride.

All strengths of Procainamide Hydrochloride contain calcium silicate, carnauba wax, NF; diethyl phthalate, NF; dimethyl polysiloxane fluid; ethylcellulose, NF; hydroxypropyl methylcellulose 2910, USP; magnesium stearate NF, and vanillin, NF. The individual strengths contain additional ingredients as follows:

500 mg: D&C Red No. 30, aluminum lake; hydroxypropyl methylcellulose, USP; polyethylene glycol, NF; polysorbate 80, NF; and titanium dioxide, USP.

750 mg: D&C Yellow No. 10, aluminum lake; FD&C Yellow No. 6, aluminum lake; hydroxypropyl methylcellulose, USP; polyethylene glycol, NF; polysorbate 80, NF; and titanium dioxide, USP.

1000 mg: FD&C Red No. 40, aluminum lake; polyethylene glycol, NF; polysorbate 80, NF;

80, NF, and titanium dioxide USP.

750 mg: D&C Yellow No. 10, aluminum lake; FD&C Yellow No. 6, aluminum lake; hydroxypropyl methylcellulose, USP; polyethylene glycol, NF; polysorbate 80, NF; and titanium dioxide, USP.

1000 mg: FD&C Red No. 40, aluminum lake; polyethylene glycol, NF; polysorbate 80, NF; and titanium dioxide, USP.

CLINICAL PHARMACOLOGY: Procainamide (PA) increases the effective refractory period of the atria, and to a lesser extent the bundle of His-Purkinje system and ventricles of the heart. It reduces impulse conduction velocity in the atria, His-Purkinje fibers, and ventricular muscle, but has variable effects on the atrioventricular (A-V) node, a direct slowing action and a weaker vagolytic effect which may speed A-V conduction slightly. Myocardial excitability is reduced in the atria, Purkinje fibers, papillary muscles, and ventricles by an increase in the threshold for excitation, combined with inhibition of ectopic pacemaker activity by retardation of the slow phase of diastolic depolarization, thus decreasing automaticity especially in ectopic sites. Contractility of the undamaged heart is usually not affected by therapeutic concentrations, although slight reduction of cardiac output may occur, and may be significant in the presence of myocardial damage. Therapeutic levels of PA may exert vagolytic effects and produce slight acceleration of heart rate, while high or toxic concentrations may prolong A-V conduction time or induce A-V block, or even cause abnormal automaticity and spontaneous firing, by unknown mechanisms.

Procainamide Hydrochloride Extended-release Tablets, are designed to provide the biopharmaceutic characteristics of a sustained and relatively constant rate of release and absorption, independent of dose, primarily from the small intestine.

The electrocardiogram may reflect these effects by showing slight sinus tachycardia (due to the anticholinergic action) and widened QRS complexes and, less regularly, prolonged Q-T and P-R intervals (due to longer systole and slower conduction), as well as some decrease in QRS and T wave amplitude. These direct effects of PA on electrical activity, conduction, responsiveness, excitability and automaticity are characteristic of a Group 1A, antiarrhythmic agent, the prototype for which is quinidine; PA effects are very similar. However, PA has weaker vagal blocking action than does quinidine, does not induce alpha-adrenergic blockade, and is less depressing to cardiac contractility.

Ingested PA is resistant to digestive hydrolysis, and the drug is well absorbed from the entire small intestinal surface, but individual patients vary in their completeness of absorption of PA. Following oral administration every 6 hours procainamide hydrochloride extended-release tablets achieve a mean steady state of procainamide (as well as N-acetylprocainamide) serum concentrations approximately equivalent to those from a comparable dose of an immediate-release dosage form given every three hours. Procainamide hydrochloride extended-release tablets result in a significantly later time-to-peak plasma concentration when compared to immediate-release dosage forms. About 15 to 20 percent of PA is reversibly bound to plasma proteins, and considerable amounts are more slowly and reversibly bound to tissues of the heart, liver, lung, and kidney. The apparent volume of distribution eventually reaches about 2 liters per kilogram body weight with a half-time of approximately five minutes. While PA has been shown in the dog to cross the blood-brain barrier, it did not concentrate in the brain at levels higher than in plasma. It is not known if PA crosses the placenta. Plasma esterases are far less active in hydrolysis of PA than of procaine. The half-time for elimination is three to four hours in patients with normal renal function, but reduced creatinine clearance and advancing age each prolong the half-time of elimination of PA.

A significant fraction of circulating PA may be metabolized in hepatocytes to N-acetylpro-

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A significant fraction of circulating PA may be metabolized in hepatocytes to N-acetylprocainamide (NAPA), ranging from 16 to 21 percent of an administered dose in "slow acetylators" to 24 to 33 percent in "fast acetylators". Since NAPA also has significant antiarrhythmic activity and somewhat slower renal clearance than PA, both hepatic acetylation rate capability and renal function, as well as age, have significant effects on the effective biologic half-time of therapeutic action of administered PA and the NAPA derivative. Trace amounts may be excreted in the urine as free and conjugated p-aminobenzoic acid, 30 to 60 percent as unchanged PA, and 6 to 52 percent as the NAPA derivative. Both PA and NAPA are eliminated by active tubular secretion as well as by glomerular filtration. Action of PA on the central nervous system is not prominent, but high plasma concentrations may cause tremors. While therapeutic plasma levels for PA have been reported to be 3 to 10 mcg/mL certain patients, such as those with sustained ventricular tachycardia, may need higher levels for adequate control. This may justify the increased risk of toxicity (see OVERDOSAGE). Where programmed ventricular stimulation has been used to evaluate efficacy of PA in preventing recurrent ventricular tachyarrhythmias, higher plasma levels (mean, 13.6 mcg/mL) of PA were found necessary for adequate control.

INDICATIONS AND USAGE:
Procainamide Hydrochloride Extended-release Tablets are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided. Initiation of procainamide treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

Because procainamide has the potential to produce serious hematological disorders (0.5 percent), particularly leukopenia or agranulocytosis (sometimes fatal), its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment clearly outweigh the risks. (See WARNINGS and Boxed Warning.)

CONTRAINDICATIONS:
Complete Heart Block: Procainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during PA treatment without evidence of A-V conduction appearing, PA should be stopped. In cases of second degree A-V block or various types of hemiblock, PA should be avoided or discontinued because of the possibility of increased severity of block, unless the ventricular rate is controlled by an electrical pacemaker.

Idiosyncratic Hypersensitivity: In patients sensitive to procaine or other ester-type local anesthetics, cross sensitivity to

cainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during PA treatment without evidence of A-V conduction appearing, PA should be stopped. In cases of second degree A-V block or various types of hemiblock, PA should be avoided or discontinued because of the possibility of increased severity of block, unless the ventricular rate is controlled by an electrical pacemaker.

Idiosyncratic Hypersensitivity: In patients sensitive to procaine or other ester-type local anesthetics, cross sensitivity to PA is unlikely; however, it should be borne in mind, and PA should not be used if it produces acute allergic dermatitis, asthma, or anaphylactic symptoms.

Lupus Erythematosus: An established diagnosis of systemic lupus erythematosus is a contraindication to PA therapy, since aggravation of symptoms is highly likely.

Torsades de Pointes: In the unusual ventricular arrhythmia called "les torsades de pointes" (twisting of the points), characterized by alternation of one or more ventricular premature beats in the directions of the QRS complexes on ECG in persons with prolonged Q-T and often enhanced U waves, Group 1A antiarrhythmic drugs are contraindicated. Administration of PA in such cases may aggravate this special type of ventricular extrasystole or tachycardia instead of suppressing it.

WARNINGS:

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any antiarrhythmic agent to have a significant risk in patients with structural heart disease.

Blood Dyscrasias: Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia and thrombocytopenia have been reported in patients receiving procainamide hydrochloride at a rate of approximately 0.5%. Most of these patients received procainamide hydrochloride within the recommended dosage range. Fatalities have occurred (with approximately 20-25 percent mortality in reported cases of agranulocytosis). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts including white cell, differential and platelet counts be performed at weekly intervals for the first three months of therapy; and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat or stomatitis), bruising or bleeding. If any of these hematologic disorders are identified, procainamide hydrochloride should be discontinued. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type (see ADVERSE REACTIONS).

Digitalis Intoxication: Caution should be exercised in the use of procainamide in arrhythmias associated with digitalis intoxication. Procainamide can suppress digitalis-induced arrhythmias; however, if there is concomitant

Group 1A antiarrhythmic drugs are contraindicated. Administration of PA in such cases may aggravate this special type of ventricular extrasystole or tachycardia instead of suppressing it.

WARNINGS:

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any antiarrhythmic agent to have a significant risk in patients with structural heart disease.

Blood Dyscrasias: Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia and thrombocytopenia have been reported in patients receiving procainamide hydrochloride at a rate of approximately 0.5%. Most of these patients received procainamide hydrochloride within the recommended dosage range. Fatalities have occurred (with approximately 20-25 percent mortality in reported cases of agranulocytosis). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts including white cell, differential and platelet counts be performed at weekly intervals for the first three months of therapy; and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat or stomatitis), bruising or bleeding. If any of these hematologic disorders are identified, procainamide hydrochloride should be discontinued. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type (see ADVERSE REACTIONS).

Digitalis Intoxication: Caution should be exercised in the use of procainamide in arrhythmias associated with digitalis intoxication. Procainamide can suppress digitalis-induced arrhythmias; however, if there is concomitant marked disturbance of atrioventricular conduction, additional depression of conduction and ventricular asystole or fibrillation may result. Therefore, use of procainamide should be considered only if discontinuation of digitalis, and therapy with potassium, lidocaine, or phenytoin are ineffective.

First Degree Heart Block: Caution should be exercised also if the patient exhibits or develops first degree heart block while taking PA, and dosage reduction is advised in such cases. If the block persists despite dosage reduction, continuation of PA administration

must be evaluated on the basis of current benefit versus risk of increased heart block.

Predigitalization for Atrial Flutter or Fibrillation: Patients with atrial flutter or fibrillation should be cardioverted or digitalized prior to PA administration to avoid enhancement of A-V conduction which may result in ventricular rate acceleration beyond tolerable limits. Adequate digitalization reduces but does not eliminate the possibility of sudden increase in ventricular rate as the atrial rate is slowed by PA in these arrhythmias.

Congestive Heart Failure: For patients in congestive heart failure, and those with acute ischemic heart disease or cardiomyopathy, caution should be used in PA therapy, since even slight depression of myocardial contractility may further reduce cardiac output of the damaged heart.

Concurrent Other Antiarrhythmic Agents: Concurrent use of PA with other Group 1A antiarrhythmic agents such as quinidine or disopyramide may produce enhanced prolongation of conduction or depression of contractility and hypotension, especially in patients with cardiac decompensation. Such use should be reserved for patients with serious arrhythmias unresponsive to a single drug and employed only if close observation is possible.

Renal Insufficiency: Renal insufficiency may lead to accumulation of high plasma levels from conventional oral doses of PA, with effects similar to those of overdosage (see OVERDOSAGE), unless dosage is adjusted for the individual patient.

Myasthenia Gravis: Patients with myasthenia gravis may show worsening of symptoms from PA due to its procaine-like effect on diminishing acetylcholine release at skeletal muscle motor nerve endings, so that PA administration may be hazardous without optimal adjustment of anticholinesterase medications and other precautions.

PRECAUTIONS:

General: Immediately after initiation of PA therapy, patients should be closely observed for possible hypersensitivity reactions, especially if procaine or local anesthetic sensitivity is suspected, and for muscular weakness if myasthenia gravis is a possibility.

In conversion of atrial fibrillation to normal sinus rhythm by any means, dislodgement of mural thrombi may lead to embolization, which should be kept in mind.

After approximately two days, steady state plasma PA levels are produced following regular oral administration of a given dose of procainamide hydrochloride extended-release tablets at set intervals. After achieving and maintaining therapeutic plasma concentrations and satisfactory electrocardiographic and clinical responses, continued frequent periodic monitoring of vital signs and electrocardiograms is advised. If evidence of QRS widening of more than 25 percent or marked prolongation of the Q-T interval occurs, concern for overdosage is appropriate, and reduction in dosage is advisable if a 50 percent increase occurs. Elevated serum creatinine or urea nitrogen, reduced creatinine clearance, or history of renal insufficiency, as well as use in older patients (over age 60), provide grounds to anticipate that less than the usual dosage and longer time intervals between doses may suffice, since the urinary elimination of PA and NAPA may be reduced, leading to gradual accumulation beyond normally predicted amounts. If facilities are available for measurement of plasma PA and NAPA, or acetylation capability, individual dose adjustment for optimal therapeutic levels may be easier, but close observation of clin-

vals between doses may suffice, since the urinary elimination of PA and NAPA may be reduced, leading to gradual accumulation beyond normally predicted amounts. If facilities are available for measurement of plasma PA and NAPA, or acetylation capability, individual dose adjustment for optimal therapeutic levels may be easier, but close observation of clinical effectiveness is the most important criterion.

In the longer term, periodic complete blood counts are useful to detect possible idiosyncratic hematologic effects of PA on neutrophil, platelet or red cell homeostasis; agranulocytosis has been reported to occur occasionally in patients on long-term PA therapy. A rising titer of serum ANA may precede clinical symptoms of the lupoid syndrome (see Boxed Warning and ADVERSE REACTIONS). If the lupus erythematosus-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controlled by other agents, corticosteroid suppressive therapy may be used concomitantly with PA. Since the PA-induced lupoid syndrome rarely includes the dangerous pathologic renal changes, PA therapy may not necessarily have to be stopped unless the symptoms of serositis and the possibility of further lupoid effects are of greater risk than the benefit of PA in controlling arrhythmias. Patients with rapid acetylation capability are less likely to develop the lupoid syndrome after prolonged PA therapy.

Information for Patients: The physician is advised to explain to the patient that close cooperation in adhering to the prescribed dosage schedule is of great importance in controlling the cardiac arrhythmia safely. The patient should understand clearly that more medication is not necessarily better and may be dangerous, that skipping doses or increasing intervals between doses to suit personal convenience may lead to loss of control of the heart problem, and that "making up" missed doses by doubling up later may be hazardous.

The patient should be encouraged to disclose any past history of drug sensitivity, especially to procaine or other local anesthetic agents, or aspirin, and to report any history of kidney disease, congestive heart failure, myasthenia gravis, liver disease, or lupus erythematosus.

The patient should be counseled to report promptly any symptoms of arthralgia, myalgia, fever, chills, skin rash, easy bruising, sore throat or sore mouth, infections, dark urine or icterus, wheezing, muscular weakness, chest or abdominal pain, palpitations, nausea, vomiting, anorexia, diarrhea, hallucinations, dizziness, or depression.

The patient should be advised not to break or chew the tablet as this would interfere with designed dissolution characteristics. The tablet matrix of Procainamide Hydrochloride Extended-release Tablets may be seen in the stool since it does not disintegrate following release of procainamide.

Laboratory Tests: Laboratory tests such as complete blood count (CBC), electrocardiogram, and serum creatinine or urea nitrogen may be indicated, depending on the clinical situation, and periodic rechecking of the CBC and ANA may be helpful in early detection of untoward reactions.

Drug Interactions: If other antiarrhythmic drugs are being used, additive effects on the heart may occur with PA administration, and dosage reduction may be necessary (see WARNINGS).

Anticholinergic drugs administered concurrently with PA may produce additive antivagal effects on A-V nodal conduction, although this is not as well documented for PA as for quinidine.

Patients taking PA who require neuromuscular blocking agents such as succinylcholine may require less than usual doses of the latter, due to PA effects on reducing acetylcholine release.

Drug/Laboratory Test Interactions: Supratherapeutic concentrations of lidocaine and meprobamate may inhibit fluorescence of PA and NAPA, and propranolol shows a native fluorescence close to the PA/NAPA peak wavelengths, so that tests which depend on fluorescence

require less than usual doses of the latter, due to PA effects on reducing acetylcholine release.

Drug/Laboratory Test Interactions: Supratherapeutic concentrations of lidocaine and meprobamate may inhibit fluorescence of PA and NAPA, and propranolol shows a native fluorescence close to the PA/NAPA peak wavelengths, so that tests which depend on fluorescence measurement may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals have not been performed.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C: Animal reproduction studies have not been conducted with PA. It also is not known whether PA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PA should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Both PA and NAPA are excreted in human milk, and absorbed by the nursing infant. Because of the potential for serious adverse reactions in nursing infants, a decision to discontinue nursing or the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Cardiovascular System: Hypotension following oral PA administration is rare. Hypotension and serious disturbances of cardiorhythm such as ventricular asystole or fibrillation are more common after intravenous administration (see OVERDOSAGE, WARNINGS). Second degree heart block has been reported in 2 of almost 500 patients taking PA orally.

Multisystem Effects: A lupus erythematosus-like syndrome of arthralgia, pleural or abdominal pain, and sometimes arthritis, pleural effusion, pericarditis, fever, chills, myalgia, and possibly related hematologic or skin lesions (see below) is fairly common after prolonged PA administration, perhaps more often in patients who are slow acetylators (see Boxed Warning and PRECAUTIONS). While some series have reported less than 1 in 500, others have reported the syndrome in up to 30 percent of patients on long-term oral PA therapy. If discontinuation of PA does not reverse the lupoid symptoms, corticosteroid treatment may be effective.

Hematologic System: Neutropenia, thrombocytopenia, or hemolytic anemia may rarely be encountered. Agranulocytosis has occurred after repeated use of PA, and deaths have been reported. (see WARNINGS and Boxed Warning).

Skin: Angioneurotic edema, urticaria, pruritus, flushing, and maculopapular rash have also occurred occasionally.

Gastrointestinal System: Anorexia, nausea, vomiting, abdominal pain, bitter taste, or diarrhea may occur in 3 to 4 percent of patients taking oral procainamide. Hepatomegaly with increased serum aminotransferase activity have been reported after a single oral dose.

Nervous System: Dizziness or giddiness, weakness, mental depression, and psychosis with hallucinations have been reported occasionally.

OVERDOSAGE:

Progressive widening of the QRS complex, prolonged Q-T and P-R intervals, lowering of the R and T waves, as well as increasing A-V block, may be seen with doses which are excessive for a given patient. Increased ventricular extrasystoles, or even ventricular tachycardia or fibrillation may occur. After intravenous administration but seldom after oral therapy, transient high plasma levels of PA may induce hypotension, affecting systolic more than diastolic pressures, especially in hypertensive patients. Such high levels may also produce central nervous depression, tremor, and even respiratory depression.

Plasma levels above 10 mcg/mL are increasingly associated with toxic findings, which are seen occasionally in the 10 to 12 mcg/mL range, more often in the 12 to 15 mcg/mL range, and commonly in patients with plasma levels greater than [illegible]. A single oral dose

excessive for a given patient. Increased ventricular extrasystoles, or even ventricular tachycardia or fibrillation may occur. After intravenous administration but seldom after oral therapy, transient high plasma levels of PA may induce hypotension, affecting systolic more than diastolic pressures, especially in hypertensive patients. Such high levels may also produce central nervous depression, tremor, and even respiratory depression.

Plasma levels above 10 mcg/mL are increasingly associated with toxic findings, which are seen occasionally in the 10 to 12 mcg/mL range, more often in the 12 to 15 mcg/mL range, and commonly in patients with plasma levels greater than 15 mcg/mL. A single oral dose of 2 g may produce overdosage symptoms, while 3 g may be dangerous, especially if the patient is a slow acetylator, has decreased renal function, or underlying organic heart disease.

Treatment of overdosage or toxic manifestations includes general supportive measures, close observation, monitoring of vital signs and possibly intravenous pressor agents and mechanical cardiorespiratory support. If available, PA and NAPA plasma levels may be helpful in assessing the potential degree of toxicity and response to therapy. Both PA and NAPA are removed from the circulation by hemodialysis but not peritoneal dialysis. No specific antidote for PA is known.

DOSAGE AND ADMINISTRATION: The oral dose and interval of administration should be adjusted for the individual patient, based on clinical assessment of the degree of underlying myocardial disease, the patient's age, and renal function.

As a general guide, for younger patients with normal renal function, an initial total daily oral dose of up to 50 mg/kg of body weight of procainamide hydrochloride extended-release tablets may be used, given in divided doses, every six hours, to maintain therapeutic blood levels. For older patients, especially those over 50 years of age, or for patients with renal, hepatic, or cardiac insufficiency, lesser amounts or longer intervals may produce adequate blood levels, and decrease the probability of occurrence of dose related adverse reactions.

To provide up to 50 mg per kg of body weight per day *

Patients Weighing	Dosage
88-110 lb (40-50 kg)	500 mg q6 hours
132-154 lb (60-70 kg)	750 mg q6 hours
176-198 lb (80-90 kg)	1 g q6 hours
>220 lb (>100 kg)	1.25 g q6 hours

* Initial dosage schedule guide only, to be adjusted for each patient individually, based on age, cardiorenal function, blood level (if available), and clinical response.

HOW SUPPLIED:
Procainamide Hydrochloride Extended-release Tablets, USP, 500 mg (capsule-form, pink, scored, film-coated, debossed COPLEY 188) are supplied as follows: Bottles of 100 – NDC 38245-188-10 and Bottles of 500 – NDC 38245-188-50.

Procainamide Hydrochloride Extended-release Tablets, USP, 750 mg (capsule-form, tan, scored, film-coated, debossed COPLEY 114) are supplied as follows: Bottles of 100 – NDC 38245-114-10 and Bottles of 500 – NDC 38245-114-50.

Procainamide Hydrochloride Extended-release Tablets, USP, 1000 mg (capsule-form, red, scored, film-coated, debossed Copley 117) are supplied as follows: Bottles of 100-NDC 38245-117-10 and Bottles of 250 – NDC 38245-117-25.

Storage Conditions:
Protect from moisture. Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Revised: January 1996
LEA500000

Manufactured by:
COPLEY PHARMACEUTICAL, INC.
Canton, MA 02021

and NAPA are removed from the circulation by hemodialysis but not peritoneal dialysis. No specific antidote for PA is known.

DOSAGE AND ADMINISTRATION: The oral dose and interval of administration should be adjusted for the individual patient, based on clinical assessment of the degree of underlying myocardial disease, the patient's age, and renal function.

As a general guide, for younger patients with normal renal function, an initial total daily oral dose of up to 50 mg/kg of body weight of procainamide hydrochloride extended-release tablets may be used, given in divided doses, every six hours, to maintain therapeutic blood levels. For older patients, especially those over 50 years of age, or for patients with renal, hepatic, or cardiac insufficiency, lesser amounts or longer intervals may produce adequate blood levels, and decrease the probability of occurrence of dose related adverse reactions.

To provide up to 50 mg per kg of body weight per day *	
Patients Weighing	Dosage
88-110 lb (40-50 kg)	500 mg q6 hours
132-154 lb (60-70 kg)	750 mg q6 hours
176-198 lb (80-90 kg)	1 g q6 hours
>220 lb (>100 kg)	1.25 g q6 hours

* Initial dosage schedule guide only, to be adjusted for each patient individually, based on age, cardiorenal function, blood level (if available), and clinical response.

HOW SUPPLIED:
Procainamide Hydrochloride Extended-release Tablets, USP, 500 mg (capsule-form, pink, scored, film-coated, debossed COPLEY 188) are supplied as follows: Bottles of 100 – NDC 38245-188-10 and Bottles of 500 – NDC 38245-188-50.

Procainamide Hydrochloride Extended-release Tablets, USP, 750 mg (capsule-form, tan, scored, film-coated, debossed COPLEY 114) are supplied as follows: Bottles of 100 – NDC 38245-114-10 and Bottles of 500 – NDC 38245-114-50.

Procainamide Hydrochloride Extended-release Tablets, USP, 1000 mg (capsule-form, red, scored, film-coated, debossed Copley 117) are supplied as follows: Bottles of 100-NDC 38245-117-10 and Bottles of 250 – NDC 38245-117-25.

Storage Conditions:
Protect from moisture. Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Revised: January 1998
LEA500000

Manufactured by:
COPLEY PHARMACEUTICAL, INC.
Canton, MA 02021

ANDA 40-111

SEP 14 1995

Copley Pharmaceutical Inc.
Attention: Bernie Grubstein
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Mr. Grubstein:

Reference is made to the bioequivalence and dissolution data submitted on July 5, 1994, for Procainamide Hydrochloride Extended-release Tablets USP, 1.0 gm.

The Office of Generic Drugs (OGD) has reviewed the bioequivalence studies comparing the test product Procainamide HCL Extended-release Tablets USP, 1.0 gm, lot B-10012 and B-03314, manufactured by Copley Pharmaceutical Inc. with the reference listed drug Procain®, lot 31163D, manufactured by Parke Davis and found them to be incomplete for the following reason:

> As specified in the Office of Generic Drugs Guidance, Oral Extended (Controlled) Release Dosage Forms *in vivo* Bioequivalence and *in vitro* Dissolution testing dated, September 9, 1993, a single dose, fasting study, single dose non-fasting study and a multiple dose steady state study are required as a condition of approval for Extended-release dosage forms. A multiple dose steady state study will be required as a condition of approval for this product. If you want to deviate from the guidance, documented evidence has to be provided so that the Agency can make intelligent judgement regarding your request.

The dissolution data indicates that more than of the drug is dissolved in 8 hours. Please provide a detailed explanation, including data describing why the USP Procainamide Hydrochloride SR dissolution 'test 5' for a 500 mg product was selected rather than dissolution 'test 6' for the 750 mg product.

An action described under 21 CFR 314.96 which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290.

In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 12 1995

Procainamide Hydrochloride
1.0gm ER Tablet
ANDA 40-111
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40111A.794

Copley Pharmaceutical Inc.
Canton, MA-02021
Submission Date:
July 5, 1994

AN AMENDMENT TO THE REVIEW

I.BACKGROUND : Procainamide is a class IA type antiarrhythmic agent. On July 5, 1994 the firm submitted an application consisting of A] Single dose Fasting and B] A single dose "food challenge" bio-equivalency studies comparing 1000mg test (Copley) and reference (Parke Davis's Procan^{R} SR) tablet formulations along with C] Dissolution testing methodology and data comparing the test and the reference formulations. **In addition, the firm was seeking a waiver for the steady state multiple dose bio-study.** Copley Pharmaceuticals, Inc. already had the agency's approval for the 500mg and 750mg extended release tablets and was seeking the approval for its 1000mg ER tablet formulation.

In a review dated February 28, 1995, the Division noticed the following Deficiencies and Recommendations:

"DEFICIENCIES :

1. The firm has not conducted a comparative "multiple dose" study to compare the test and the reference formulations under the steady state. The firm may refer to the Guidance for "Oral Extended (Controlled) release dosage forms in vivo bioequivalence and in vitro dissolution testing". A copy of the guidance could be obtained from the Division of Bioequivalence, Office of Generic Drugs.

2. The firm should comment on why it chose to comply with the USP Procainamide HCl SR dissolution test 5 for 500mg instead of say dissolution test 6 for 750mg. The dissolution data indicates that more than of the drug is dissolved in 8hr. Also, if dose strength is any criterion, the reviewer feels that a test for 750mg will be more appropriate than a test resembling 500mg strength.Please provide additional information and data to support claim for Test 5, 500mg vs Test 6, 750mg.

RECOMMENDATIONS :

1. The fasting and "food challenge" single dose bioequivalency studies conducted by Copley Pharmaceuticals on its 1000mg Procainamide Hydrochloride SR tablet, comparing it to Procan^{R}, 1000mg SR tablet has been found acceptable by the Division of Bioequivalence. However the application is incomplete.

2. The firm however has not conducted an acceptable in-vivo

multiple dose bioequivalency study. From the bioequivalence point of view, the application is incomplete. The request for waiver of in-vivo multiple dose study is denied. Sponsor agrees with the provided data for waiver.

3. The dissolution testing data conducted by Copley Pharmaceuticals on its Procainamide Hydrochloride 1000mg SR tablet, lot # 117Z02 is acceptable. The dissolution specifications however could be finalized only when the firm provides additional information required as per Deficiency 2.

4. The firm should submit additional information as stated in Deficiency 1-2".

II.COMMENTS : The current amendment states the rationale behind the above recommendations:

1. The firm is seeking a bio-study waiver for highest strength multiple dose study.

2. The Division neither had nor has any pharmacokinetic data on the 1000mg steady state scenario where the steady state indices such as i) Fluctuation, ii) Swing etc. are ascertained, whereby a comparability judgement could have been made for the test and reference formulations.

3. Procainamide has an active metabolite N-Acetyl Procainamide for which the comparative steady state parameters for 1000mg formulation are not known.

4. If the firm is seeking a multiple dose bio-study waiver for the 1000mg formulation for the safety concerns, it should state so and provide the necessary safety/toxicity information (either from the literature or in-house source).

5. If subject safety is the issue for the drug study, can a multiple dose scenario be studied in a small subject population consisting of rapid metabolizers (fast acetylators), in a pilot study to ascertain the steady state equivalence? If not, can it be studied in small number of patients who are already at steady state?

6. Recently, in simulations conducted by Dr.Andre Jackson for 500mg SR procainamide formulations, for a comparison of single dose vs multiple dose kinetics (Generics and Bioequivalence, Edited by Andre Jackson, Chapter 2, CRC press, 1994, p 29-47), he could observe the reduction of confidence interval limits as could be expected for a linear scenario. This behavior could however may change if the kinetics at or around 1000mg becomes non-linear. Therefore if possible, the information for the linearity of kinetics at single and multiple dose at 1000mg should be provided.

III.RECOMMENDATIONS :

1. A request for bio-study waiver for the multiple dose bioequivalency study for the 1000mg procainamide SR formulation could be reconsidered provided the firm satisfactorily addresses comments 4, 5 and 6.

2. Comments 4, 5 and 6 should be sent to the firm.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY RPATNAIK
FT INITIALED BY RPATNAIK 8/10/95

Concur: Date: 9/12/95
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #40-111 (Original, Duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Patnaik, Sathe), Drug File, Division File.

FEB 28 1995

Procainamide Hydrochloride
1.0gm ER Tablet
ANDA 40-111
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40111SDW.794

Copley Pharmaceutical Inc.
Canton, MA-02021
Submission Date:
July 5, 1994

REVIEW OF TWO BIO-STUDIES AND THE DISSOLUTION DATA

I.INTRODUCTION : Procainamide is a class IA type antiarrhythmic agent. It exerts the pharmacologic action by altering the membrane conductance of sodium cations, depression of phase-0 depolarization and slow conduction velocity in the Purkinje fibers to a moderate degree at normal resting potential values (Vm). Chemically it is p-amino-N(2-(diethylamino)-ethyl)-benzamide monohydrochloride with a molecular weight 271.79. The monohydrochloride is soluble in water.

Procainamide is quickly and nearly completely absorbed after oral administration to normal subjects, the bioavailability fraction being about 83%. The peak levels are seen within 45-75 min. after ingestion of drug. It is about 20% bound to plasma proteins. The apparent volume of distribution is about 2lit/kg. The major metabolic pathway involves N-acetylation which yields a pharmacologically active metabolite N-acetyl procainamide (NAPA). NAPA is seen in equal or more concentrations than the parent drug. Elimination is both by renal as well as non-renal routes. The clearance depends on the acetylation phenotype. Up to 70% of the dose is eliminated unchanged in the urine. Being a weak base, the changes in urine pH cause alterations in the renal excretion. The mean half-life of the drug is approximately 3.0hr.

II.CURRENT SUBMISSION : The current application consists of A] Single dose Fasting and "food challenge" bio-equivalency studies comparing 1000mg test (Copley) and reference (Parke Davis's Procan® SR) tablet formulations and B] Dissolution testing methodology and data comparing the test and the reference formulations. **In addition, the firm is seeking a waiver for the steady state multiple dose bio-study.** Copley Pharmaceuticals, Inc. already has the agency approval for the 500mg and 750mg extended release tablets and is now seeking the approval for its 1000mg ER tablet formulation.

III.COMPOSITION OF THE FORMULATIONS : The composition of the test formulation is given in Table I-1. From the composition it is clear that Procainamide Hydrochloride is the principal and largest component. The release mechanism appears to be diffusion. Hydroxypropyl Methyl Cellulose, Ethyl Cellulose and Carnauba Wax appear to be the release retardants. Magnesium Stearate is the lubricant, Dimethyl polysiloxane is a prosthetic aid, Calcium Silicate is an excipient and Vanillin is the flavor.

Table I-1

Granulation Ingredients:	**mg/tab**	**Prodn. Scale Up**
Procainamide HCl	1000.0	
Magnesium Stearate		
Carnauba Wax		
Ethyl Cellulose		
Calcium Silicate (Syn)		
Dimethylphthalate		
Coating Ingredients:		
Isopropyl Alcohol		
Dimethyl Polysiloxane		
Purified Water		
Hydroxypropylmethyl Cellulose		
Vanillin		
Opadry--Red		
Total Weight	1207.75mg	

* Removed during processing

** Opadry--Red consists of

Hydroxypropylmethyl Cellulose
FD & C Red No.L40
Polyethylene Glycol
Titanium Dioxide
Polysorbate 80

** Total Opadry--Red

IV.BIO-STUDY NO.B-10012, BIOEQUIVALENCY STUDY :

A. TITLE : A relative bioavailability study of Procainamide Hydrochloride (1000mg) extended release tablets.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORIES :

1a. Principal Study Investi
1b. Medical Investigator

2. Bio-Study Site and La

3. Analytical Investigator :

4. Analytical Site and L

C. STUDY OBJECTIVE : To compare the relative bioavailability of

procainamide hydrochloride extended release 1000mg tablets (Copley Pharmaceuticals, Inc.) with that of Procan® SR 1000mg tablets (Parke-Davis) in healthy male volunteers under fasting conditions.

D. STUDY DESIGN AND NUMBER OF SUBJECTS : This was a single dose two-way crossover study in 24 healthy male volunteers with a one week washout period. Twenty-six (26) subjects were recruited with the idea to complete the study with at least twenty-four (24) subjects. All twenty-six subjects were dosed in Period I of the study. Twenty-five of the twenty-six subjects completed the study. Subject #09, failed to report to the clinical research unit for period II dosing and was withdrawn from the study. In its place samples of subject #26, who happened to have the same sequence were analyzed. The serum samples from 24 (Twenty-four) subjects were assayed.

E. SUBJECT SELECTION/EXCLUSION CRITERIA :

Volunteers were included in the study if they met the following requirements:

1. Males between the ages 18-41, weighing between 135-220 pounds with individual weight variation not more than ±10% for height and body frame.

2. Volunteers succesfully completing the General physical Examination criterion for clinical measurements. The clinical chemistry measurements criterion included: Hemoglobin, Hematocrit, RBC count, creatinine, BUN, glucose, SGOT, SGPT, total bilirubin and alkaline phosphatase. The urine analysis included specific gravity, protein, glucose, ketone, bilirubin, occult blood and cells. Also an HIV 1 and 2 screen and a Hepatitis screen were performed.

Volunteers were excluded from the study for the following:

1. History of chronic alcohol consumption, drug addiction or serious gastrointestinal, renal, hepatic, neurological, respiratory, endocrine, ocular, hematological, psychological or cardiovascular disease.

2. Clinical laboratory values falling outside the normal range even after retesting.

3. History of allergic responses to the class of drug being tested.

4. Subjects using tobacco in any form.

5. Subjects whose urine analysis indicates presence of any of the drugs of abuse.

6. Subjects who have donated blood less than a month prior to the start of the study.

7. Subjects who have taken an investigational drug within 30 days prior to the start of the study.

8. Subjects exposed to known hepatic enzyme inducing or inhibition agents within 30 days prior to dosing.

9. Subjects with a history of poor acetylation.

F. SUBJECT RESTRICTIONS : The following restrictions were put on the subjects throughout the study:

1. No other medication including the OTC products, in two weeks prior to the start of the study.

2. No consumption of caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate and caffeine containing sodas, colas etc.) for at least 3 days prior to days on which they are to be dosed and during the periods when blood samples are being obtained.

3. No consumption of alcohol from at least two days prior to days on which they are to be dosed and during the periods when blood samples are being obtained.

The volunteers violating any of the above restrictions could be excluded or dropped from the study at the discretion of the clinical investigator.

G. STUDY SCHEDULES :

1. **Methods** : On study days 1 and 8, a single dose of 1000mg of either the test or the reference formulations was administered to each fasting volunteer. Meals (Lunch 4hr after the dose) and fluid intake were controlled during each 34hr confinement period. The heart rate of each study participant was monitored at prior to dosing, and at 2, 4, 6 and 12hr after the dose while the blood pressure was monitored at prior to dose and at 6 and 12hr after each dose.

2. **Randomization Schedule** :

Treatment Phase I	Treatment Phase II	Volunteer Number
A	B	1, 4, 6, 8, 11, 12, 15, 16, 18, 19, 22, 23, 25
B	A	2, 3, 5, 7, 9, 10, 13, 14, 17, 20, 21, 24, 26

3. **Blood Sampling** : Serial blood samples, (10ml each time) were obtained at Pre-dose (0hr) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 30.0 and 36.0hr following the ingestion of dose. The samples were allowed to clot, the serum samples were separated and frozen and stored at or below -20^{0}C until shipment for the analysis.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Procainamide Hydrochloride oral SR Tablet, 1000mg (Copley Pharm.), Lot #117Z02, Assay Potency=98.5%, Batch Size-

2. REFERENCE PRODUCT B : Procan^{R} oral SR Tablet, 1000mg (Parke-Davis), Lot #31163D, Assay Potency=99.8%, Expiry date: 05/95

I. ASSAY METHODOLOGY : **The following assay methodology may be a proprietary information of the firm and therefore should not be released under the F.O.I.**

J. PHARMACOKINETICS AND STATISTICS : The analytical data was used to calculate the following pharmacokinetic parameters: $AUC_{(0-t)}$, $AUC_{(0-inf)}$, Cmax, Tmax, Kelm and $T_{1/2}$. The pharmacokinetic parameters and serum levels were statistically evaluated by ANOVA for differences due to treatments, study days, dosing sequence and subjects within sequence. The 90% confidence interval (Two-one sided test) was used using LSMEANS and standard error of estimate for comparing the mean pharmacokinetic parameters.

K. RESULTS OF THE BIOEQUIVALENCY STUDY : The mean serum levels of procainamide corresponding to the test and reference treatments are given in Table 1.1. A comparative evaluation of the mean pharmacokinetic parameters of procainamide is given in Table 1.2. The mean serum levels of N-Acetyl procainamide corresponding to the test and the reference treatments are given in Table 1.3. A comparative evaluation of the mean pharmacokinetic parameters of N-Acetyl procainamide is given in Table 1.4. For the sake of convenience the figures are rounded off to two digits. The mean serum concentration vs time plots for the drug and the metabolite are given in Attachments 1.5 and 1.6 respectively.

Table 1.1: Procainamide mean serum levels (ug/ml) with %CV, (N=24)

Time(hr)	Test (Copley)	Reference (Parke-Davis)
0.0	0.0 (--)	0.0 (--)
0.5	0.625 (34.2)	0.655 (32.0)
1.0	1.111 (21.1)	1.195 (24.7)
1.5	1.345 (17.6)	1.447 (15.1)
2.0	1.491 (16.2)	1.622 (15.0)
2.5	1.657 (15.2)	1.780 (15.4)
3.0	1.698 (16.3)	1.847 (16.7)
3.5	1.687 (19.0)	1.846 (15.9)
4.0	1.713 (23.5)	1.796 (17.3)
5.0	1.554 (23.5)	1.665 (21.8)
6.0	1.321 (27.6)	1.389 (21.2)
8.0	1.014 (22.7)	1.034 (20.6)
10.0	0.763 (19.9)	0.744 (22.6)
12.0	0.585 (26.9)	0.536 (23.3)
16.0	0.364 (23.5)	0.335 (31.5)
24.0	0.175 (34.0)	0.151 (34.2)
30.0	0.075 (68.6)	0.055 (88.6)
36.0	0.009 (232.6)	0.012 (202.1)

Table 1.2 : Procainamide LSMEAN Parameters (N=24)

PK Parameter	Test	Reference	90% Con.Int.
AUC_{0-t}, ug*hr/ml	18.58	18.63	97.1-102
AUC_{0-inf}, ug*hr/ml	19.44	19.44	97.5-102
Cmax, ug/ml	1.86	1.94	92.9-99
Tmax, hr	3.15	3.13	------
$T_{1/2}$, hr	6.36	6.10	------
$LnAUC_{0-t}$	2.91	2.91	96.9-103
$LnAUC_{0-inf}$	2.95	2.95	97.3-103
LnCmax	0.60	0.65	92.5-98.2

Table 1.3: N-Acetyl Procainamide mean serum levels (ug/ml) with %CV's, (N=24)

Time(hr)	Test (Copley)	Reference (Parke-Davis)
0.0	0.0 (--)	0.0 (--)
0.5	0.116 (76.8)	0.120 (62.6)
1.0	0.257 (42.2)	0.266 (47.5)
1.5	0.363 (47.7)	0.378 (39.1)
2.0	0.426 (45.2)	0.458 (40.9)
2.5	0.496 (42.6)	0.537 (38.4)
3.0	0.559 (39.3)	0.611 (37.0)
3.5	0.602 (38.5)	0.659 (36.2)
4.0	0.653 (38.6)	0.681 (35.1)
5.0	0.680 (34.2)	0.733 (34.6)
6.0	0.654 (34.2)	0.698 (36.3)
8.0	0.639 (34.7)	0.654 (36.1)
10.0	0.603 (31.6)	0.626 (36.0)
12.0	0.538 (33.0)	0.544 (37.0)
16.0	0.425 (38.8)	0.411 (39.4)
24.0	0.286 (37.7)	0.276 (42.8)
30.0	0.190 (42.1)	0.178 (42.3)
36.0	0.113 (54.0)	0.108 (47.0)

Table 1.4 : N-Acetyl Procainamide LSMEAN Parameters (N=24)

PK Parameter	Test (Copley)	Reference (Parke Davis)	90% Con.Int.
AUC_{0-t}, ug*hr/ml	13.68	13.81	95.8-102.3
AUC_{0-inf}, ug*hr/ml	15.70	15.54	97.4-104.6
Cmax, ug/ml	0.70	0.75	90.6-98.2
Tmax, hr	5.58	5.00	-------
$T_{1/2}$, hr	11.28	10.71	-------
$LnAUC_{0-t}$	2.56	2.57	95.7-102.3
$LnAUC_{0-inf}$	2.69	2.69	96.8-104.4
LnCmax	-0.40	-0.34	90.5-97.9

L. COMMENTS ON THE BIOEQUIVALENCY STUDY : The mean test and reference levels of procainamide and N-acetyl procainamide are comparable along with the percent coefficient of variation. The untransformed and log transformed confidence intervals of all the mean pharmacokinetic parameters for both the drug and the active metabolite are well within the limits of the two one sided test suggesting the equivalence of the two formulations under the single dose fasting state. AUC_{0-t} values of procainamide and N-acetyl procainamide data are more than 95% and 87% of the AUC_{0-inf} values indicating adequacy of the sampling duration. The Cmax and Tmax values are similar suggesting comparable absorption.

M. ADVERSE EVENTS : A total of 15 adverse events were reported in eight out of twenty-six subjects in both periods, out of which 10 are for the reference formulation and the rest for the test formulation. The events which occurred with almost similar frequency in both periods, included headache, diarrhea, pain, fatigue, dyspepsia, hypesthesia, hypertonia and pharyngitis and did not result in any dropouts. All the events were categorized as mild and no countermeasures were necessary to address them.

V. BIO-STUDY NO.B-03314, POST PRANDIAL STUDY

A. TITLE : A relative bioavailability food effect study of procainamide hydrochloride (1000mg) extended-release tablets.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1a. Principal Investigator
1b. Medical Investigator

2. Bio-Study Site and Lab

3. Analytical Investigator :

4. Analytical Site and Lab

C. STUDY OBJECTIVES : To compare the relative bioavailability of procainamide hydrochloride extended release 1000mg tablets (Copley Pharmaceutical, Inc.) with that of Procan^{R} SR 1000mg tablets (Parke Davis) in healthy adult male volunteers under non-fasting conditions. A second objective is to compare the bioavailability of the test product when dosed under non-fasting conditions to when dosed under fasting conditions.

D. STUDY DESIGN : This was a three way crossover study in 18 healthy male subjects with a one week washout period between the two treatments. Eighteen (18) subjects entered the study and all of them completed the study without any dropouts.

E. SUBJECT SELECTION/EXCLUSION CRITERIA : Similar to study No.B-10012, Fasting Study.

F. SUBJECT RESTRICTIONS : Similar to study No.B-10012, Fasting Study.

G. STUDY SCHEDULES :

1. **Methods** : Each study subject was dosed on three different occasions depending on the randomization sequence. At 15 minutes before dosing, those subjects to be dosed under "fed" state were served a standard breakfast consisting of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hashbrown potatoes, six fluid oz. (180ml) of orange juice and eight fluid oz. (240ml) of whole milk. The breakfast was similar in quality and content for both fed periods. No fluid except for that given with the drug administration or standard breakfast were allowed 1hr before dosing until 2hr after dosing.

2. **Randomization Schedule** : Subjects were randomized to the following six sequences :

Treatments			
Phase I	Phase II	Phase III	Volunteer Number
A	B	C	5, 10, 15
A	C	B	1, 9, 16
B	C	A	6, 7, 12
B	A	C	8, 11, 18
C	A	B	4, 14, 17
C	B	A	2, 3, 13

3. **Blood Sampling** : Ten (10)ml venous blood was collected in vacutainers with no anticoagulant at pre-dose (0)hr and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 30.0, and 36.0hr following the dose. After clotting, the blood samples were centrifuged to separate serum samples. The serum samples were stored at -20^{0}C until analysis.

H. DRUG TREATMENTS :

1. PRODUCT A : Procainamide Hydrochloride, 1000mg SR Tablet (Copley Pharm.) without food, Lot #117Z02, Assay Potency=98.5%, Batch Size=

2. PRODUCT B : Procainamide Hydrochloride, 1000mg SR Tablet (Copley Pharm.) with food, Lot #117Z02, Assay Potency=98.5%, Batch Size=

3. PRODUCT C : Procan^R Tablet, 1000mg SR (Parke Davis) with food, Lot #31163D, Assay Potency=99.8%, Expiry date: 05/95

I. ASSAY METHODOLOGY : Similar to the previous study.

J. PHARMACOKINETICS AND STATISTICS : The pharmacokinetic and statistical data were similarly treated as in the previous study.

K. RESULTS OF THE POST PRANDIAL BIO-STUDY : The mean serum levels of procainamide corresponding to the three treatments are given in Table 2.1. A comparative evaluation of the mean pharmacokinetic parameters of procainamide is given in Table 2.2. The mean serum levels of N-Acetyl procainamide corresponding to the three treatments are given in Table 2.3. A comparative evaluation of the

mean pharmacokinetic parameters of N-Acetyl procainamide is given in Table 2.4. The concentrations are measured as ug/ml, the AUC's as ug*hr/ml, Cmax as ug/ml, Tmax as hr. The mean serum level time plots for the drug and the metabolite are given in Attachments 2.5 and 2.6 respectively.

Table 2.1: Procainamide mean serum levels (ug/ml) with %CV,(N=18)

Time(hr)	TRTMNT.A (COPLEY,FAST)	TRTMNT.B (COPLEY, FOOD)	TRTMNT.C (PARKE-DAVIS,FOOD)
0.0	0.0 (--)	0.0 (--)	0.0 (--)
0.5	0.601 (44.8)	0.356 (88.9)	0.390 (110.2)
1.0	1.154 (36.5)	0.997 (45.6)	1.044 (45.9)
1.5	1.489 (30.6)	1.445 (36.1)	1.517 (23.8)
2.0	1.641 (26.5)	1.590 (26.5)	1.722 (19.8)
2.5	1.803 (21.9)	1.674 (23.1)	1.742 (20.2)
3.0	1.723 (19.9)	1.694 (18.9)	1.803 (18.4)
3.5	1.674 (22.8)	1.724 (20.2)	1.814 (18.1)
4.0	1.617 (19.4)	1.745 (17.8)	1.742 (17.7)
5.0	1.403 (23.3)	1.763 (17.0)	1.773 (18.4)
6.0	1.169 (22.7)	1.460 (19.9)	1.470 (19.7)
8.0	0.918 (24.4)	1.030 (23.4)	1.103 (29.5)
10.0	0.718 (27.4)	0.811 (24.9)	0.785 (25.5)
12.0	0.550 (29.8)	0.617 (27.9)	0.571 (27.3)
16.0	0.377 (32.2)	0.380 (25.7)	0.343 (33.7)
24.0	0.167 (38.0)	0.142 (47.4)	0.129 (51.6)
30.0	0.069 (65.6)	0.048 (85.9)	0.039 (96.0)
36.0	0.012 (233.4)	0.004 (424.3)	0.004 (412.3)

Table 2.2: Procainamide LSMEAN PK Parameters, (N=18)

PK Param.	Test, Fast	Test, Food	Ref, Food	(T/R)*100
AUC_{0-t}	17.99	18.80	18.68	101
AUC_{0-inf}	18.76	19.54	19.41	101
Cmax,ug/ml	1.89	1.89	1.95	97
Tmax (hr)	2.67	3.39	3.17	107
$LnAUC_{0-t}$	2.87	2.91	2.90	101^{+}
$LnAUC_{0-inf}$	2.91	2.95	2.946	101^{+}
LnCmax	0.62	0.62	0.65	96.7^{+}

$^{+}$ = Ratio of antilogs of Geometric means.

Table 2.3: N-Acetyl Procainamide mean serum levels (ug/ml) with %CV's, (N=18)

Time(hr)	TRTMNT.A (COPLEY,FAST)	TRTMNT.B (COPLEY, FOOD)	TRTMNT.C (PARKE-DAVIS,FOOD)
0.0	0.0 (--)	0.0 (--)	0.0 (--)
0.5	0.137 (65.0)	0.044 (146.9)	0.054 (145.4)
1.0	0.322 (45.0)	0.190 (68.3)	0.199 (62.8)
1.5	0.491 (46.5)	0.338 (55.0)	0.333 (49.4)
2.0	0.553 (36.5)	0.404 (46.8)	0.438 (45.6)
2.5	0.652 (34.3)	0.466 (45.3)	0.491 (44.3)
3.0	0.700 (34.8)	0.523 (42.4)	0.555 (41.8)
3.5	0.743 (32.4)	0.581 (41.1)	0.610 (39.4)
4.0	0.774 (34.5)	0.656 (43.5)	0.644 (39.0)
5.0	0.806 (35.7)	0.740 (38.7)	0.758 (40.0)
6.0	0.752 (34.4)	0.752 (35.8)	0.769 (38.5)
8.0	0.728 (32.5)	0.725 (33.8)	0.748 (34.9)
10.0	0.695 (31.1)	0.725 (34.0)	0.726 (36.6)
12.0	0.632 (31.9)	0.635 (35.8)	0.642 (33.5)
16.0	0.530 (34.3)	0.532 (34.3)	0.511 (35.0)
24.0	0.345 (39.4)	0.331 (35.7)	0.315 (37.7)
30.0	0.229 (43.1)	0.226 (43.4)	0.203 (41.0)
36.0	0.148 (47.4)	0.147 (53.3)	0.126 (42.2)

Table 2.4 : N-Acetyl Procainamide LSMEAN Parameters, (N=18)

P K Parameter	Copley, Test (Fasting)	Copley, Test (Food)	Parke Davis, Ref. (Food)	(Test/Ref) *100
AUC_{0-t} (ug*hr/ml)	16.46	15.74	15.42	102
AUC_{0-inf} (ug*hr/ml)	18.86	17.36	17.29	100
Cmax (ug/ml)	0.84	0.81	0.81	100
Tmax (hr)	4.94	6.89	6.56	105
$LnAUC_{0-t}$	2.75	2.70	2.67	103[+]
$LnAUC_{0-inf}$	2.87	2.79	2.79	100[+]
LnCmax	-0.24	-0.27	-0.28	101[+]

[+] = Ratio of antilogs of Geometric means.

L. COMMENTS FOR THE POST PRANDIAL BIO-STUDY : The mean procainamide and N-acetyl procainamide levels along with their respective percent coefficient of variation are comparable. The pharmacokinetic point estimates are similar and the ratios of the test to reference parameters are close to 1 after the food treatment. There is no indication of dose dumping due to food. The Cmax's and AUC's are comparable with and without food treatment indicating that food has not altered the extent of absorption.

M. ADVERSE EFFECTS : The adverse effects included headache, malaise, nausea, vomiting and in two cases hypochromic anemia. A total of 18 adverse effects were reported in 7 subjects in 3 periods. The intensity of the adverse effects was mild, none of them was serious and all except hypochromic anemia were resolved without any therapy. The adverse effects were distributed randomly and similarly to all three treatments.

VI. DISSOLUTION METHODOLOGY : The following methodology was used for the comparative dissolution of the test and the reference procainamide hydrochloride SR formulations.

Apparatus: USP XXII Apparatus II (paddle)
Speed: 50rpm
Medium: 0.1N HCl and Phosphate Buffer pH 7.5
Volume: 1000ml in both cases

The dissolution method is as per USP procainamide hydrochloride SR

tablet dissolution Test #5 for the 500mg strength tablets (p.1296). The firm has used 1000ml volume as specified in "Method B under Delayed release (Enteric Coated) Articles--General Drug Release Standard" of USP 23 (p.1796).

A. RESULTS OF THE DISSOLUTION TESTING : The dissolution results are documented in Table D1.

B. COMMENT ABOUT THE DISSOLUTION TESTING :

Even though dissolution testing is acceptable as per USP 23 Test 5 for 500mg tablet, it is not known why the firm chose this particular test compared to say Test 6 for 750mg. If strength is any criterion, the reviewer feels that a test for 750mg will be more appropriate than a test resembling 500mg strength. Also, the comparative cumulative percent dissolved in 480mins for both the test and the reference formulations is greater than the USP limit set for the 750mg tablet for 8hr duration.

VII.OVERALL COMMENTS :

1. The dissolution method and comparative data for both formulations appears within the USP specified limits however the firm should respond to deficiency 2 before the specs are finalized.

2. The comparative fasting and "food challenge" bioequivalency studies are acceptable.

3. The firm has **not** conducted a comparative "multiple dose" study on the test and the reference formulations.

4. Even though the inclusion/exclusion criterion suggests a subject screen for the poor metabolizers, the frequency distribution of Cmax, AUCt and AUCinf for N-acetyl procainamide for the fasting study clearly indicated a bimodal distribution. This being a bioequivalence study, however, this phenomenon seen in the same subjects for both treatments may not alter the overall outcome of the study results.

5. The observed half-life of the drug is almost twice that of the literature reported values.

6. In the fasting study, the individual procainamide and n-acetyl procainamide serum levels are comparable except for the multiple peaks seen in some cases.

7. In the "food challenge" study, there was no significant food effect on the extent of absorption. Also, no dose dumping was observed due to food.

VIII.DEFICIENCIES :

1. The firm has not conducted a comparative "multiple dose" study to compare the test and the reference formulations under the steady state. The firm may refer to the Guidance for "Oral Extended (Controlled) release dosage forms in vivo bioequivalence and in vitro dissolution testing". A copy of the guidance could be obtained from the Division of Bioequivalence, Office of Generic Drugs.

2. The firm should comment on why it chose to comply with the USP Procainamide HCl SR dissolution test 5 for 500mg instead of say dissolution test 6 for 750mg. The dissolution data indicates that more than of the drug is dissolved in 8hr. Also, if dose strength is any criterion, the reviewer feels that a test for 750mg will be more appropriate than a test resembling 500mg strength.Please provide additional information and data to support claim for Test 5, 500mg vs Test 6, 750mg.

VIII.RECOMMENDATIONS :

1. The fasting and "food challenge" single dose bioequivalency studies conducted by Copley Pharmaceuticals on its 1000mg Procainamide Hydrochloride SR tablet, comparing it to Procan^{R}, 1000mg SR tablet has been found acceptable by the Division of Bioequivalence. However the application is incomplete.

2. The firm however has not conducted an acceptable in-vivo multiple dose bioequivalency study. From the bioequivalence point of view, the application is incomplete. The request for waiver of in-vivo multiple dose study is denied.

3. The dissolution testing data conducted by Copley Pharmaceuticals on its Procainamide Hydrochloride 1000mg SR tablet, lot # 117Z02 is acceptable. The dissolution specifications however could be finalized only when the firm provides additional information required as per Deficiency 2.

4. The firm should submit additional information as stated in Deficiency 1-2.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY AJJACKSON
FT INITIALED BY AJJACKSON 2/13/95

Table D1. In Vitro Dissolution Testing

Drug (Generic Name): Procainamide Hydrochloride, sustained release
Dose Strength: 1.0gm
ANDA No.: 40-111
Firm: Copley Pharmaceuticals Inc.
Submission Date: July 5, 1994

I. Conditions for Dissolution Testing:

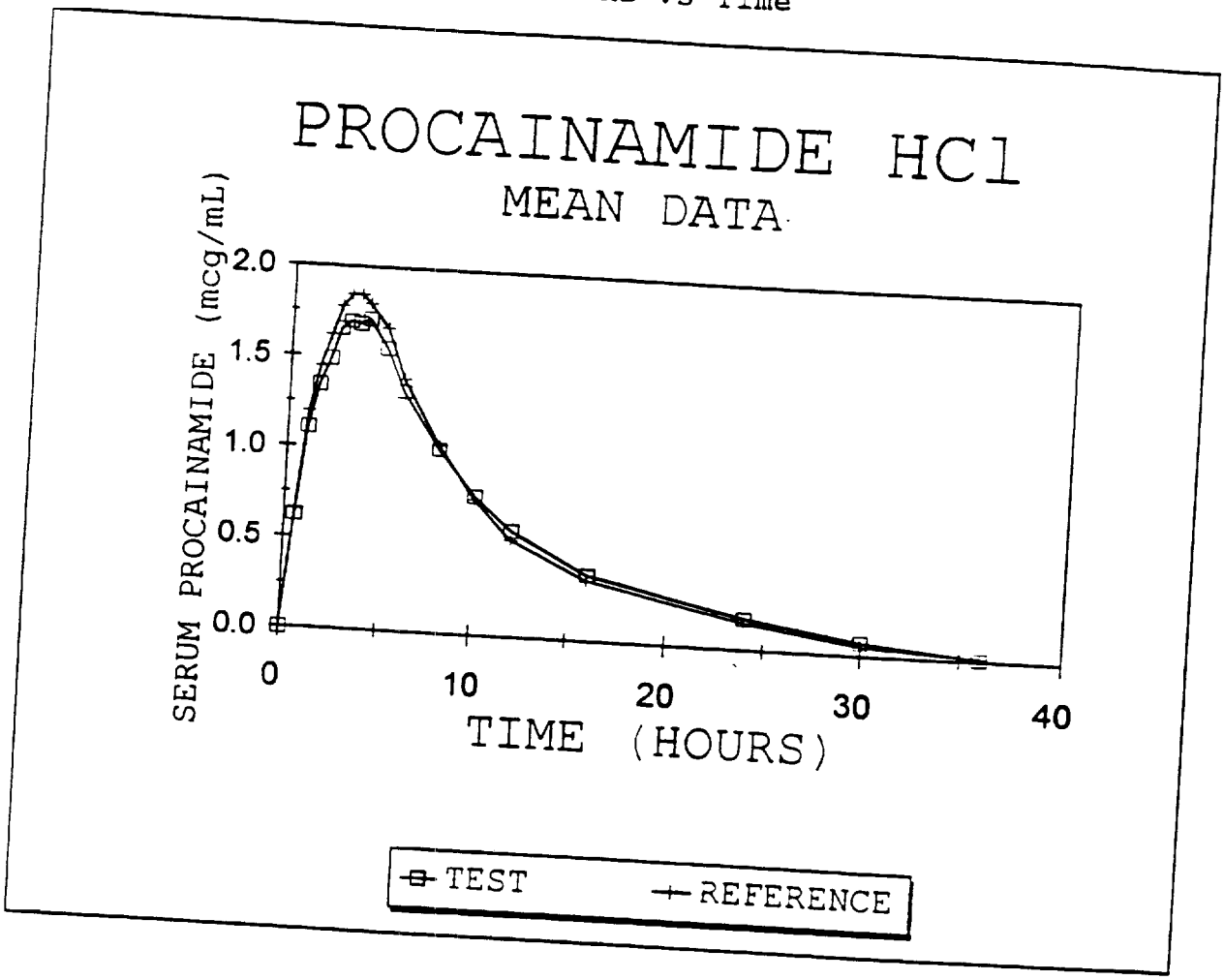
USP XXII Paddle: Method II RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl at 1hr and pH 7.5 Phosphate buffer at 2, 4, 6 and 8hr, Volume: 1000ml for both medias.
Specifications: at 1hr within at 4hr within at 6hr NLT and at 8hr NLT
Reference Drug: Procan® SR tablet by Parke Davis
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Procainamide Hydrochloride SR Tablet Lot # 117Z02 Strength (1000mg)			Reference Product: Procan® SR tablet Lot # 31163D Strength (1000mg)		
0.1N HCl	Mean %	Range	%CV	Mean %	Range	%CV
15	18.9		3.2	19.2		14.1
30	27.3		1.8	28.7		2.1
45	33.0		1.2	34.7		1.7
60	37.6		1.6	39.2		1.5
Phosphate Buffer pH 7.5						
120	51.6		1.0	53.3		1.1
240	65.8		1.0	68.2		1.0
360	75.1		0.7	77.6		1.0
480	81.7		1.3	84.2		1.1

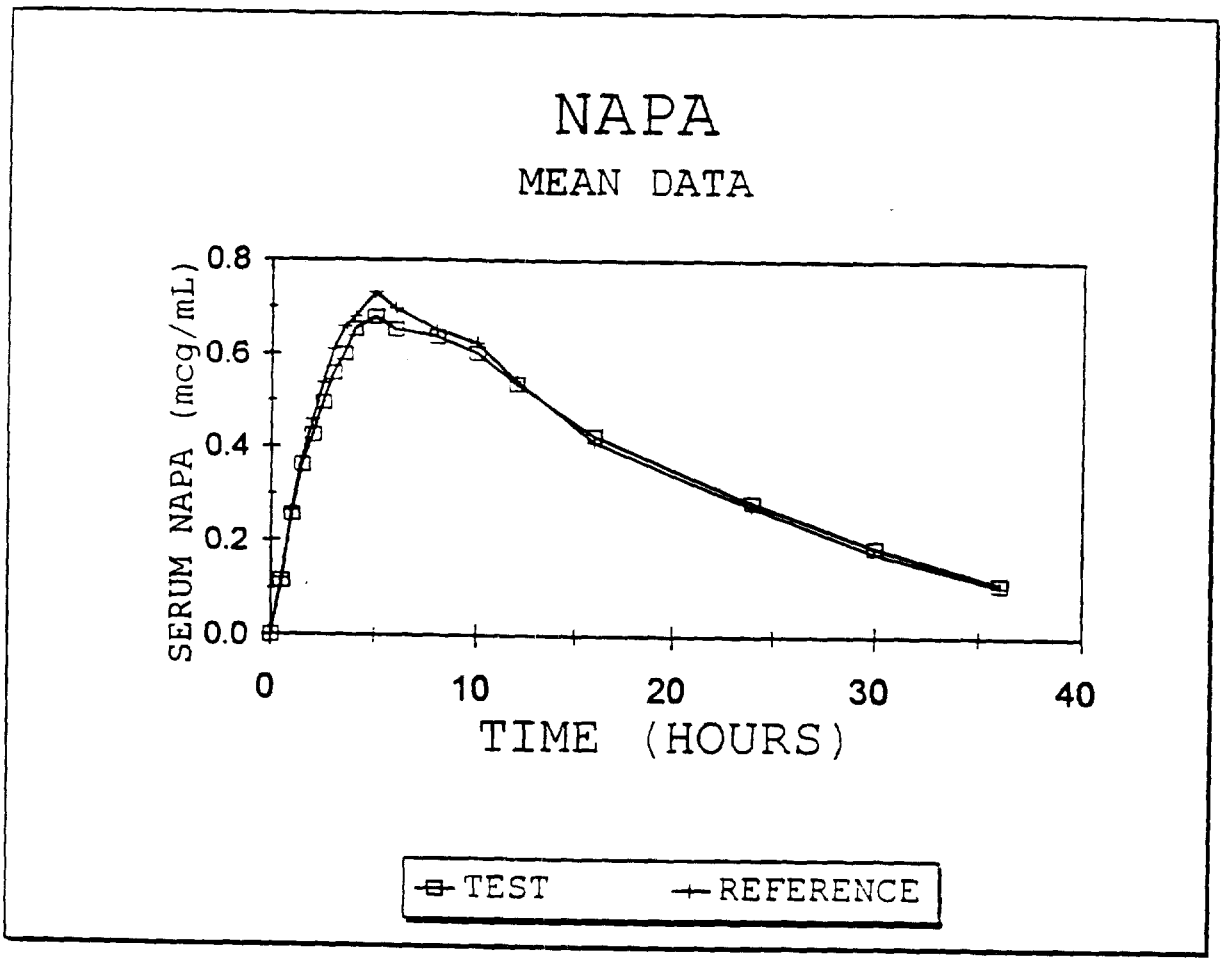
Attachment 1.5

Figure 4.5.1 Linear Plot of Mean Serum Drug Concentrations *vs* Time



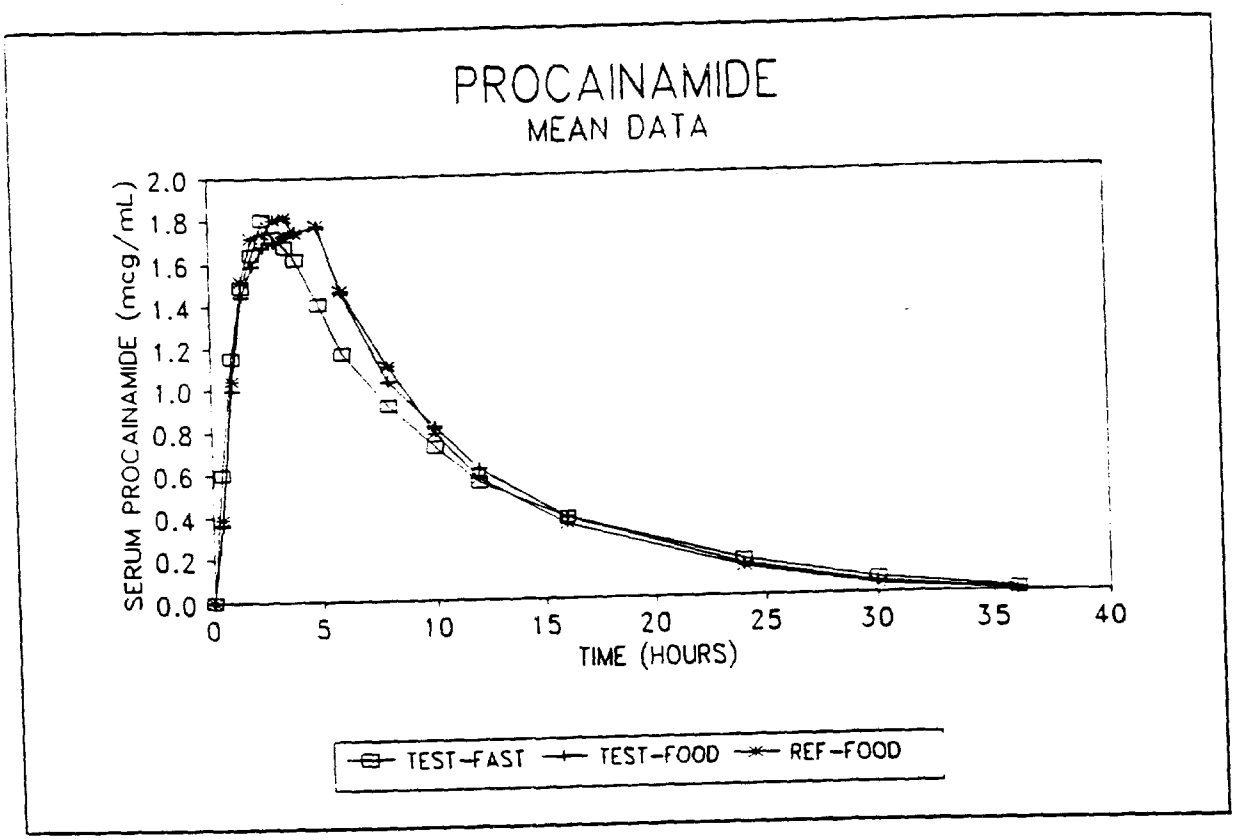
Attachment 1-6

Figure 4.5.3 Linear Plot of Mean Serum Metabolite Concentrations vs Time



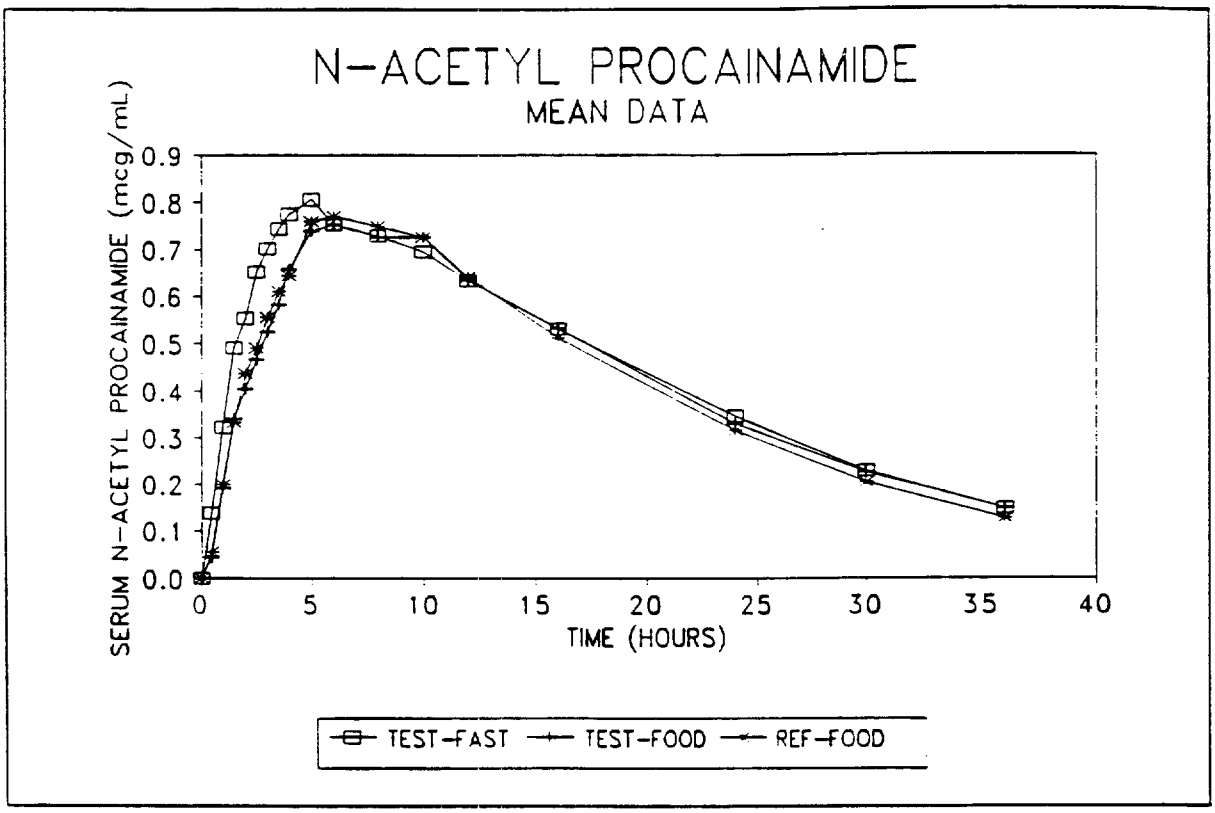
000154

Attachment 2.5



001242

Attachment 2-6



001244

ANDA 40-111

Copley Pharmaceutical Inc.
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton MA 02021

OCT 29 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Procainamide Hydrochloride Extended-release Tablets USP, 1.0 gm.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 25 1996

Procainamide Hydrochloride
1.0gm ER Tablet
ANDA 40-111
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40111SD.496

Copley Pharmaceutical Inc.
Canton, MA-02021
Submission Date:
April 19, 1996

REVIEW OF A MULTIPLE DOSE BIO-STUDY AND DISSOLUTION INFORMATION

I.INTRODUCTION : Procainamide is a class IA type antiarrhythmic agent. It exerts the pharmacologic action by altering the membrane conductance of sodium cations, depression of phase-0 depolarization and slow conduction velocity in the Purkinje fibers to a moderate degree at normal resting potential values (Vm). Chemically it is p-amino-N(2-(diethylamino)-ethyl)-benzamide monohydrochloride with a molecular weight 271.79. The monohydrochloride is soluble in water.

Procainamide is quickly and nearly completely absorbed after oral administration to normal subjects, the bioavailability fraction being about 83%. The peak levels are seen within 45-75 minutes after ingestion of drug. It is about 20% bound to plasma proteins. The apparent volume of distribution is about 2 liters/kg. The major metabolic pathway involves N-acetylation which yields pharmacologically active N-acetyl procainamide (NAPA) metabolite. NAPA levels are equal or more than the parent drug. Elimination is both by renal as well as non-renal routes. The clearance depends on the acetylation phenotype. Up to 70% of the dose is eliminated unchanged in the urine. Being a weak base, the changes in urine pH cause alterations in the renal excretion. The mean half-life of the drug is approximately 3.0hr.

II.BACKGOUND : The firm had submitted an application for the above mentioned formulation on July 5, 1994. The application consisted of A] Single dose 'fasting' and a single dose "food challenge" bio-equivalency studies comparing 1000mg test (Copley) and reference (Parke Davis's Procan^{R} SR) tablet formulations and B] Dissolution testing methodology and data comparing the test and the reference formulations. **The firm was seeking a waiver for the steady state multiple dose bio-study.** In a letter dated 9/14/95, the division denied the waiver request and asked Copley Pharmaceuticals, Inc. either to provide reasons why a multiple dose study cannot be conducted on its 1000 mg ER formulation or to conduct a multiple dose study. Also, the firm was asked to clarify its position on the dissolution method it had used.

III.CURRENT APPLICATION : The current application consists of the multiple dose study results comparing firm's 1000 mg ER formulation with the reference Parke Davis's 1000 mg Procan^{R} SR formulation. The firm has provided the rationale behind the selection of the dissolution method and is seeking approval for its revised dissolution methodology and specifications.

III.COMPOSITION OF THE FORMULATION : To better facilitate the review, the composition of the test formulation is given in Table I-1. From the composition it is clear that Procainamide Hydrochloride is the principal and largest component. The release mechanism appears to be diffusion. Hydroxypropyl Methyl Cellulose, Ethyl Cellulose and Carnauba Wax appear to be the release retardants. Magnesium Stearate is the lubricant, Dimethyl polysiloxane is a prosthetic aid, Calcium Silicate is an excipient and Vanillin is the flavor.

Table I-1

Granulation Ingredients:	**mg/tab**	**Prodn. Scale Up**
Procainamide HCl	1000.0	
Magnesium Stearate		
Carnauba Wax		
Ethyl Cellulose		
Calcium Silicate (Syn)		
Dimethylphthalate		
Coating Ingredients:		
Isopropyl Alcohol		
Dimethyl Polysiloxane		
Purified Water		
Hydroxypropylmethyl Cellulose		
Vanillin		
Opadry--Red		
Total Weight	1207.75mg	

* Removed during processing

** Opadry--Red consists of

Hydroxypropylmethyl Cellulose
FD & C Red No.L40
Polyethylene Glycol
Titanium Dioxide
Polysorbate 80

** Total Opadry--Red

IV.BIO-STUDY NO.P95-379, MULTIPLE DOSE BIOEQUIVALENCY STUDY :

A. TITLE : A multiple dose relative bioavailability study of Procainamide Hydrochloride 1000 mg (extended release) tablets under fasting conditions.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORIES :

1a. Study Sub-Investigator
1b. Medical Investigator :

2. Bio-Study Site and Laboratory :

3. Analytical Investigator :

4. Analytical Site and Laboratory :

5. Study Dates : Period I Dec.07-09, 1995
Period II Dec.14-16, 1995

C. STUDY OBJECTIVE : To compare the relative bioavailability of procainamide hydrochloride extended release 1000mg tablets (Copley Pharmaceuticals, Inc.) with that of Procan^{R} SR 1000mg tablets (Parke-Davis, Division of Warner-Lambert Company) in healthy male volunteers under multiple dose conditions using a randomized crossover design.

D. STUDY DESIGN AND NUMBER OF SUBJECTS : This was a two-way multiple dose, open label, two-period, two-sequence crossover study in 24 healthy male volunteers with a one week washout period. Twenty-four (24) subjects were recruited in the study. All twenty-four (24) subjects were dosed in Period I of the study. Twenty-three (23) of the twenty-four (24) subjects completed the study. Subject #18, failed to report to the clinical research unit for period II dosing, secondary to an illness unrelated to the study drug and was withdrawn from the study. The serum samples from Twenty-three (23) subjects were assayed for procainamide and n-acetyl procainamide.

E. SUBJECT SELECTION/EXCLUSION CRITERIA :

Volunteers were included in the study if they met the following requirements:

1. Healthy males between the ages 18-50 inclusive. The weight range was not more than ± 15% for height and body frame as per desirable weights for men -1983, Metropolitan height and weight table. Volunteers with a body weight less than 60 kgs (132 lbs) were excluded from the study.

2. Volunteers succesfully completing the General physical Examination criterion for clinical measurements. The clinical chemistry measurements criterion included a) Hematology : Hemoglobin, Hematocrit, WBC count with differential, RBC count and platelet count, b) Clinical Chemistry : serum creatinine, BUN, glucose, SGOT, SGPT, total bilirubin and alkaline phosphatase, c) HIV 1 and HIV 2 antibody and Hepatitis B surface antigen screens, d) Urinalysis : pH, specific gravity, protein, glucose, ketone, bilirubin, occult blood and cells, e) Urine drug screen : ethyl alcohol, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite, opiates and phencyclidine.

Volunteers were excluded from the study for the following:

1. Recent history of alcohol or drug addiction or abuse.

2. Cinically significant disorders involving gastrointestinal, renal, hepatic, neurological, respiratory, endocrine, ocular, hematological, psychological or cardiovascular disease.

3. Clinical laboratory values falling outside the normal range even after retesting.

4. A positive hepatitis B surface antigen or a reactive HIV 1 and HIV 2 antibody screen.

5. History of allergic responses to the class of drug being tested.

6. Clinically significant allergies including drug allergies.

7. Clinically significant illness during the 4 weeks prior to period I dosing.

8. Subjects currently using tobacco products.

9. Subjects exposed to known hepatic enzyme inducing or inhibition agents within 30 days prior to dosing.

10. Subjects who have donated >150ml blood less than a month prior to the start of the study.

11. Subjects who have donated plasma (e.g.plasmapheresis) within 14 days prior to Period I dosing.

12. Subjects who have taken an investigational drug within 30 days prior to the start of the study.

13. Subjects who report taking any prescription drug in the 14 days prior to period I dosing.

F. SUBJECT RESTRICTIONS : The following restrictions were put on the subjects throughout the study:

1. No other medication including the OTC products, within one week prior to the start of the study.

2. No consumption of caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate and caffeine containing sodas, colas etc.) for at least 2 days prior to days on which they are to be dosed and during the confinement periods of the study.

3. No consumption of alcohol from at least two days prior to days on which they were to be dosed and during the periods when blood samples were collected.

The volunteers violating any of the above restrictions could be excluded or dropped from the study at the discretion of the clinical investigator.

G. STUDY SCHEDULES :

1. **Methods** : The study subjects were confined to study site at least 10 hours prior to dose 1 until at least 8 hours after dose 7. In every study period, depending on the randomization sequence, each study subject was administered either the test or reference 1000 mg procainamide ER formulation, in a q.8 hours dosing regimen for a total of seven doses. Each dose was administered with 240mL of water at room temperature. Subjects fasted from 10 hours prior to dose 7 administration until 4 hours after dose 7. Subjects were served standardized meals and beverages during the confinement period at the pre-specified times. The meals were same in content and quantity during each confinement period. The study flow chart is given in Attachment 'A' for convenience.

2. **Randomization Schedule** :

Treatment		
Phase I	Phase II	Volunteer Number
A	B	1, 3, 4, 6, 12, 13, 14, 18, 19, 21, 23, 24
B	A	2, 5, 7, 8, 9, 10, 11, 15, 16, 17, 20, 22

3. **Blood Sampling** : A total of eighteen (18)blood samples, (10ml each time) were collected for assay immediately prior to Dose 1, 4, 5, 6 and 7 and following dose 7 administration at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0 and 8.0hr.The samples were allowed to clot, the serum samples were separated and frozen and stored at or below -20^{0}C until shipment for the analysis.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Procainamide Hydrochloride oral ER Tablet,

1000mg (Copley Pharm.), Lot #117Z02, Assay Potency=98.5%, Batch Size=125,000 units, Expiration date : May 1996 (a 2-year expiration date has been given by Chemistry Division, as per Dr.Sema Basaran).

2. REFERENCE PRODUCT B : Procan^{R} oral SR Tablet, 1000mg (Parke-Davis), Lot #8934D, Assay Potency=100.3%, Expiry date: 01/96

I. ASSAY METHODOLOGY : **The following assay methodology may be a proprietary information of the firm and therefore should not be released under the F.O.I.**

J. PHARMACOKINETICS AND STATISTICS : The analytical data was used to calculate the following pharmacokinetic parameters: $AUC_{(0\text{-}Tau)}$, area under the curve under one dosing interval, Cmax at steady state, Tmax at steady state, Cmin at steady state, Caverage at steady state and DGF i.e. degree of fluctuation at steady state. The pharmacokinetic parameters with and without logarithmic conversion and serum levels, were statistically evaluated by ANOVA for differences due to treatments, study days, dosing sequence and subjects within sequence. The 90% confidence interval (Two-one sided test) was used with LSMEANS and standard error of estimate for comparing the mean pharmacokinetic parameters.

K. RESULTS OF THE BIOEQUIVALENCY STUDY : The mean serum levels of procainamide corresponding to the test and reference treatments are given in Table 1.1. A comparative evaluation of the mean pharmacokinetic parameters of procainamide is given in Table 1.2. The mean serum levels of N-Acetyl procainamide corresponding to the test and the reference treatments are given in Table 1.3. A comparative evaluation of the mean pharmacokinetic parameters of N-Acetyl procainamide is given in Table 1.4. The mean serum concentration vs time plots for the drug and the metabolite are given in Attachments 1.5 and 1.6 respectively.

Table 1.1: Procainamide mean serum levels (ug/ml) with (std), (N=23)

Time(hr)	Test (Copley)	Reference (Parke-Davis)
0.0	0.0 (---)	0.0 (---)
24	2.105 (0.427)	2.253 (0.601)
32	1.913 (0.396)	1.936 (0.399)
40	1.802 (0.406)	1.928 (0.554)
48	2.308 (0.418)	2.390 (0.496)
48.5	3.028 (0.641)	3.051 (0.658)
49	3.490 (0.705)	3.511 (0.665)
49.5	3.727 (0.626)	3.716 (0.670)
50	3.793 (0.618)	3.823 (0.651)
50.5	3.787 (0.545)	3.875 (0.684)
51	3.645 (0.560)	3.707 (0.613)
51.5	3.470 (0.630)	3.573 (0.583)
52	3.290 (0.605)	3.408 (0.609)
52.5	3.183 (0.616)	3.268 (0.582)
53	2.983 (0.650)	3.051 (0.599)
54	2.634 (0.578)	2.605 (0.475)
56	2.001 (0.450)	1.976 (0.419)

Table 1.2 : Procainamide LSMEAN Parameters (N=23)

PK Parameter	Test	Reference	Ratio *100	90% Con.Int.
$AUC_{0\text{-}Tau}$, ug*hr/ml	24.45	24.79	98.6	
Cmaxss, ug/ml	3.998	4.026	99.3	
Tmaxss, hr	2.074	2.028	102	
Cminss, ug/ml	2.309	2.392	96.5	
Cavgss, ug/ml	3.056	3.098	98.6	
DGFlu.	55.73	53.12	105	
$LnAUC_{0\text{-}Tau}$, *Geometric Mean	3.183, 24.12*	3.197, 24.47*	98.6*	95.5-102
LnCmaxss, *Geometric Mean	1.375, 3.954*	1.380, 3.975*	99.5*	96.3-103
LnCavgss, *Geometric Mean	1.103, 3.015*	1.118, 3.059*	98.6*	95.5-102

Table 1.3: N-Acetyl Procainamide mean serum levels (ug/ml) with (std), (N=23)

Time(hr)	Test (Copley)	Reference (Parke-Davis)
0.0	0.0 (---)	0.0 (---)
24	1.747(0.600)	1.783(0.638)
32	1.884(0.599)	1.973(0.693)
40	1.814(0.637)	1.902(0.729)
48	2.107(0.792)	2.167(0.789)
48.5	2.208(0.853)	2.230(0.818)
49	2.353(0.898)	2.392(0.860)
49.5	2.459(0.937)	2.481(0.908)
50	2.492(0.951)	2.512(0.935)
50.5	2.510(0.922)	2.577(0.926)
51	2.540(0.917)	2.597(0.933)
51.5	2.526(0.895)	2.601(0.911)
52	2.522(0.890)	2.604(0.918)
52.5	2.508(0.893)	2.603(0.931)
53	2.496(0.873)	2.567(0.887)
54	2.388(0.827)	2.437(0.864)
56	2.189(0.769)	2.231(0.810)

Table 1.4 : N-acetyl procainamide LSMEAN Parameters (N=23)

PK Parameter	Test	Reference	Ratio *100	90% Con.Int.
$AUC_{0\text{-}Tau}$, ug*hr/ml	19.249	19.696	97.7	
Cmaxss, ug/ml	2.629	2.694	97.6	
Tmaxss, hr	3.371	3.754	89.8	
Cminss, ug/ml	2.112	2.170	97.3	
Cavgss, ug/ml	2.406	2.462	97.7	
DGFlu.	22.253	21.719	102	
$LnAUC_{0\text{-}Tau}$, *Geometric Mean	2.886, 17.914*	2.912, 18.400*	97.4*	94.8-100
LnCmaxss, *Geometric Mean	0.897, 2.451*	0.924, 2.520*	97.3*	94.4-100
LnCavgss, *Geometric Mean	0.806, 2.239*	0.833, 2.300*	97.4*	94.8-100

L. COMMENTS ON THE STUDY : The mean test and reference levels of procainamide, N-acetyl procainamide and the respective standard deviations are comparable across the two formulations. The untransformed and log transformed confidence intervals of all the mean pharmacokinetic parameters for both the drug and the active metabolite are within the 80-125% regulatory limits (for log-transformed parameters) of the two one sided test, suggesting equivalence of the two formulations under the multiple dose steady state conditions. The Cmax and Tmax values are similar suggesting comparable absorption.

Though, the subject population are different, a cursary comparison of the $AUC_{0\text{-}inf}$ parameter of the fasting study to $AUC_{0\text{-}Tau}$ of procainamide and N-acetyl procainamide of the present multiple dose study indicated similar extent of absorption.

M. ADVERSE EVENTS : A total of 19 adverse events were reported in nine out of twenty-four subjects dosed in both periods. The events which occurred with similar frequency for both periods included asthenia, dizziness, headache, malaise, pharyngitis, sweating and vomiting and dyspepsia. The events did not result in any dropouts. All the events were categorized as non-serious, with mild to

moderate intensity. Though, the frequency was greater with the test formulation compared to the reference, the events were judged to have a possible or no relationship to the studied drug and in most cases no countermeasures were necessary to address them.

V.DISSOLUTION : In the current application, the firm is seeking a revision of its earlier position on the dissolution specifications. The firm is now requesting "a revision to the ANDA specification to meet USP 23, test #5 for 750 mg specifications" as against "USP 23, test #5 for 500 mg specifications" sought earlier. To support the new claim, the firm has stated that "Since the

- - that test #5 (under 750 mg tablet) is an appropriate dissolution specification for this product".

Background : USP recommends the following #5 and #6 drug release tests to be used for procainamide hydrochloride ER formulations.

Test 5 :

Apparatus: USP XXII Apparatus II (paddle)
Speed: 50rpm
Medium: 0.1N HCl and Phosphate Buffer pH 7.5
Sample Times : 1 hour, 4 hours, 6 hours and 8 hours.
Volume: 1000ml in both cases

The recommended tolerances are as follows:

For 500 mg tablet;

Time	Amount Dissolved
1hr	
4hr	
6hr	
8hr	

For 750 mg tablet;

Time	Amount Dissolved
1hr	
4hr	
6hr	
8hr	

Test 6 :

Apparatus: USP XXII Apparatus II (paddle)
Speed: 50rpm
Medium: 0.1N HCl and Phosphate Buffer pH 7.5

Volume: 1000ml in both cases
Sample Times : 1 hour, 4 hours and 8 hours.

For 500 mg tablet;

Time	Amount Dissolved
1hr	
4hr	
8hr	

For 750 mg tablet;

Time	Amount Dissolved
1hr	
4hr	
8hr	

In the original application, the firm had used the dissolution method as per USP procainamide hydrochloride ER tablet dissolution Test #5 for the 500mg strength tablets (p.1296). The firm had used 1000ml volume as specified in "Method B under Delayed release (Enteric Coated) Articles--General Drug Release Standard" of USP 23 (p.1796). In the deficiency letter dated 09/14/95, the firm was asked to provide the explanation regarding choosing drug release test #5 based on the dissolution results at 8 hours instead of say test #6 for 750mg. The firm has submitted a detailed response as seen in Attachment 'B'. Essentially, the firm has stated that the decision to go for test #5 was based on the accelerated stability data in addition to the comparative dissolution data. The firm is now proposing the dissolution specifications as per the USP Test #5 specifications recommended for 750 mg formulation.

A. RESULTS OF THE DISSOLUTION TESTING : The comparative dissolution results are documented in Table D1.

B. COMMENT ABOUT THE DISSOLUTION TESTING :

The dissolution testing is as per USP 23 Test #5 recommendations and is acceptable. The dissolved amounts meet the the USP recommended specifications for 750 mg strength.

VI.RECOMMENDATIONS :

1. The multiple dose bioequivalency study conducted by Copley Pharmaceuticals on its 1000mg Procainamide Hydrochloride ER tablet, comparing it to Procan^{R}, 1000mg SR tablet has been found acceptable by the Division of Bioequivalence.

2. The firm has previously conducted acceptable 'fasting' and 'food challenge' in-vivo bioequivalency studies (submission dated July 5, 1994), comparing the test product with Park-Davis's Procan^{R} 1000 mg SR tablet. The firm's Procainamide hydrochloride, 1000 mg ER tablet is deemed bioequivalent to Procan^{R}, 1000 mg SR tablet.

3. The dissolution testing data conducted by Copley Pharmaceuticals on its Procainamide Hydrochloride 1000mg ER tablet, lot # 117Z02 is acceptable. The dissolution testing should be conducted in 1000 ml of 0.1N HCl and 1000 ml of pH 7.5 phosphate buffer at 37^{0}C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Medium	Time (hr)	Amount Dissolved
0.1N HCl	1hr	
0.05M Phosphate Buffer at pH 7.5		
	4hr	
	6hr	
	8hr	not less than

4. From the Bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalency and in-vitro dissolution testing, and the application is acceptable.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 10/22/96

Concur: Date: 10/25/96
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA #40-111 (Original, Duplicate), HFD-652 (Y.C.Huang, Sathe), Drug File, Division File.

Table D1. In Vitro Dissolution Testing

Drug (Generic Name): Procainamide Hydrochloride, sustained release
Dose Strength: 1000 mg
ANDA No.: 40-111
Firm: Copley Pharmaceuticals Inc.
Submission Date: April 19, 1996

I. Conditions for Dissolution Testing:

USP XXII Paddle: Method II RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl at 1hr and pH 7.5 Phosphate buffer at 4, 6 and 8hr, Volume: 1000ml for both medias.
Specifications: at 1hr within at 4hr within at 6hr within and at 8hr NLT
Reference Drug: Procan[R] SR tablet by Parke Davis
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Procainamide Hydrochloride ER Tablet Lot #117Z02 Strength (1000mg)			Reference Product: Procan[R] SR tablet Lot #08934D Strength (1000mg)		
0.1N HCl	Mean %	Range	%CV	Mean %	Range	%CV
15	20.1		2.0	19.9		4.0
30	29.1		1.4	29.6		2.4
45	35.4		1.1	35.9		2.2
60	40.3		1.2	40.8		1.7
0.05M Phosphate Buffer pH 7.5						
120	56.6		1.4	57.2		2.6
240	71.6		1.3	72.2		1.4
360	81.1		1.1	81.7		1.3
480	87.2		1.3	88.1		1.2

B. Schematic 2: Subject Flow Sheet By Period

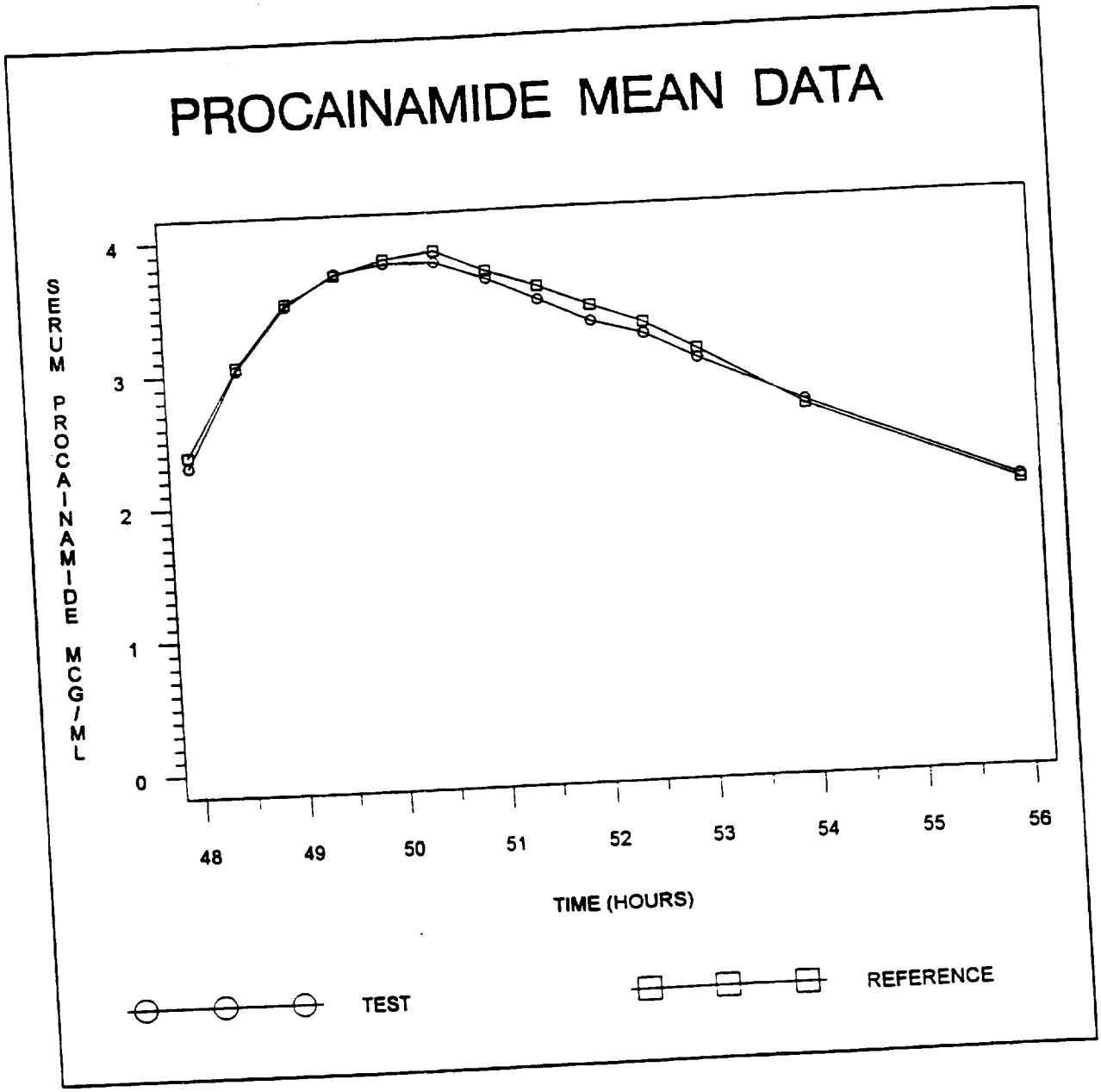
Attachment 'A'

A Relative Bioavailability Study of Procainamide 1000 mg Tablets Under Fasting Conditions

STUDY DAY	TIME	DOSE	BLOOD SAMPLE NUMBER	BLOOD COLLECTION TIME	QUERY FOR ADVERSE EVENTS	ECG	VITAL SIGNS	FLUID INTAKE	MEALS	SUBJECT INITIALS
Day -1 & 7	2100 (9:00) ** Report to Institute ** ** Site Orientation, Review of Study and Consent Document**					X				
	2330 (11:30) ** Retire **									
Day 1 & 8	0645			Wake-Up						
	0700				X		X	240 mL		
	0800	1	1	0:00				240 mL		
	1000							480 mL	Lunch	
	1215									
	1300			5:00		X		240 mL		
	1400 (2:00)							240 mL		
	1600 (4:00)	2		8:00				240 mL	Snack	
	1630 (4:30)							480 mL	Dinner	
	1815 (6:15)						X	240 mL		
	2000 (8:00)			12:00	X			240 mL	Snack	
	2230 (10:30)									
				16:00				240 mL		
Day 2 & 9	2400 (12:00)	3		24:00	X		X	240 mL		
	0800	4	2					240 mL		
	1000							480 mL	Lunch	
	1215							240 mL		
	1400 (2:00)							240 mL		
	1600 (4:00)	5	3	32:00				240 mL	Snack	
	1630 (4:30)							480 mL	Dinner	
	1815 (6:15)							240 mL		
	2000 (8:00)			36:00	X	X	X	240 mL	Snack	
	2230 (10:30)									
								240 mL		
Day 3 & 10	2400 (12:00)	6	4							
	0645			Wake-Up						
	0800	7	5	48:00	X		X			
	0830		6	48:30						
	0900		7	49:00						
	0930		8	49:30				240 mL		
	1000		9	50:00						
	1030		10	50:30						
	1100		11	51:00						
	1130		12	51:30						
	1200		13	52:00				480 mL	Lunch	
	1215									
	1230		14	52:30						
	1300 (1:00)		15	53:00						
	1400 (2:00)		16	54:00						
	1600 (4:00)		17	56:00	X	X	X			

(May leave Institute after the 56 hour blood sample collection)

Attachment 1.5



Attachment 1.6